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Transcutaneous spinal cord stimulation for restoration of upper extremity function after spinal cord injury

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Abstract

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Spinal cord injury is currently incurable. Standard of care after spinal cord injury focuses on prevention of the secondary complications and maximizing residual function. The most common site of injury is the cervical level that results in tetraplegia. Incomplete cervical injury is the most frequent neurological category. Loss of motor control and sensory function in the upper extremity is a particularly devastating aspect of cervical injuries that impairs the ability to perform activities of daily living. Restoration of hand and arm function is consistently rated as the highest treatment priority among people with tetraplegia due to cervical spinal cord injury, 5-fold higher than any other function included in the surveys. Nevertheless, current approaches to improve hand and arm function are largely ineffective. Electrical spinal cord stimulation, however, is one of the emerging neuromodulation strategies to restore motor function. The aims of this dissertation are to (1) review the applications of therapeutic electrical spinal cord stimulation after spinal cord injury, (2) determine improvements in hand and arm function resulting from non-invasive electrical cervical spinal cord stimulation, and (3) quantify long-term benefits that may persist beyond the stimulation. Therapeutic potential of transcutaneous spinal cord stimulation is evaluated in a prospective, open-label, two arm cross-over study. Intervention arms consist of intensive upper limb functional task training alone and transcutaneous electrical cervical spinal cord stimulation combined with training. The Graded Redefined Assessment of Strength, Sensation and Prehension is used as the primary outcome measure. Improvements achieved by training alone are compared to those obtained when transcutaneous spinal cord stimulation is paired with training. The findings demonstrate that transcutaneous cervical spinal cord stimulation has augmentative effect on restoration of hand and arm function. Additionally, gains are maintained up to six months without stimulation or training, suggesting that electrical stimulation can promote neuroplasticity. This dissertation provides evidence that transcutaneous spinal cord stimulation is a highly promising intervention for recovery of upper extremity function after cervical spinal cord injury, with the significant advantage of not requiring surgery.

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Plain Language Summary

Spinal cord injury is the damage to any part of the spinal cord. It interrupts the communication between the brain and the body, and generally results in lasting paralysis. The most common injury site is the neck. Neck injuries cause paralysis in both upper and lower limbs, named tetraplegia. Loss of function in the hands and arms hampers the ability to perform even simple activities of daily living. Therefore, it severely restricts independence and quality of life. There is no cure for spinal cord injury at this time.

Newly developing treatments are quite promising to restore function in people with spinal cord injury. One of the most promising treatment options is the electrical stimulation of the spinal cord. Recently, researchers showed that electrical stimulation of the injured spinal cord enables people to move their paralyzed muscles. Electrical stimulation can be delivered to the spinal cord either by surgically inserted electrodes in the body or by electrodes placed over the skin non-invasively. Up to now, most of the studies with electrical stimulation of the spinal cord focused on restoring walking ability. However, improvement of the hand and arm function is the most important treatment goal for most individuals with tetraplegia.

In this research, we investigated the treatment effect of electrical stimulation of the spinal cord on hand and arm movements. A total of seven participants were included in the study. We stimulated the spinal cord non-invasively over the skin surface. We compared the improvements resulting from intensive training alone to stimulation combined with training. Our findings showed that non-invasive electrical stimulation improves upper limb function after spinal cord injury. The improvements were both immediate and lasting. Our participants maintained their functional gains up to six months during the follow-up period without further training or electrical stimulation. These results show that non-invasive spinal cord stimulation is a highly promising treatment for restoration of upper limb function for people with spinal cord injury. Besides the benefits of this treatment on functional improvement, it also has the advantage of not requiring surgery.

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Chapter 1 Introduction

1.1 Background and motivation

Spinal cord injury (SCI) is the damage to any part of the spinal cord that interrupts communication between the brain and the body. Depending on the level and the extent of the damage, individuals with SCI usually have permanent paralysis and disability. Consequently, SCI has a life-long, high socioeconomic impact on affected individuals, families, and health care systems. Estimated global SCI incidence is 40 to 80 new cases per million population per year (WHO, 2013). Each year about 17,700 new spinal cord injuries (SCI) occur in the United States (NSCISC, 2019). The estimated direct life-time cost of cervical SCI is between $2.3 and $5.0 million that varies depending on the level, severity, and age at injury (Cao, Chen, & DeVivo, 2011; NSCISC, 2019). Additionally, indirect costs such as work loss, reduced productivity, personal assistance expenses, and the burden on the family is estimated an average of $76,000 per year (NSCISC, 2019).

Cervical injury is the most common neurologic level of SCI that constitutes 60% of all cases (NSCISC, 2019). Injury at cervical level of the spinal cord results in tetraplegia that is characterized by loss of sensory and motor function in all four limbs and an extensive range of impairments in autonomic systems. Loss of motor control and sensory function in the upper extremity is a particularly devastating aspect of SCI that results in marked limitations in the ability to perform activities of daily living (Furlan, Noonan, Singh, & Fehlings, 2011). As a consequence, hand and arm dysfunction severely restricts independence and quality of life

(Snoek, MJ, Hermens, Maxwell, & Biering-Sorensen, 2004). Not surprisingly, regaining hand and arm function is ranked consistently as the highest treatment priority among people with tetraplegia, 6-fold higher than regaining walking ability (Anderson, 2004; French, Anderson-Erisman, & Sutter, 2010; Lo, Tran, Anderson, Craig, & Middleton, 2016).

At present, there is no cure for SCI (Chen & Levi, 2017). Standard of care after SCI focuses on prevention of the secondary complications and maximizing residual function. Rehabilitation is of utmost importance and is the only currently available treatment to enhance function and independence. Exercise therapy is the mainstay of the rehabilitation that aims to restore volitional motor control and to develop adaptation strategies utilizing muscles not affected by the spinal cord lesion (Bryden, Sinnott, & Mulcahey, 2005; Hicks et al., 2003; Kapadia, Zivanovic, & Popovic, 2013; Kloosterman, Snoek, & Jannink, 2009; Lim & Tow, 2007; Medicine, 2005; Popovic et al., 2006; Thielen, Marino, Duff, Kaplan, & Mulcahey, 2018).

Despite the wide-ranging impact on independence and overall quality of life, interventions to restore hand and arm function are extremely limited, and outcomes are less than satisfactory in clinical practice (Bryden et al., 2005; Kloosterman et al., 2009; X. Lu, Battistuzzo, Zoghi, & Galea, 2015; Thielen et al., 2018). In recent years, interdisciplinary efforts for recovery of motor function gained momentum. Based on the knowledge gained from animal studies, motor learning-based rehabilitation interventions, also known as task-specific training, are augmented by combining afferent sensory stimulation (Beekhuizen & Field-Fote, 2008), advanced neuromuscular stimulation (Hoffman & Field-Fote, 2013) or transcranial direct current/magnetic stimulation (Cortes et al., 2017; Gomes-Osman & Field-Fote, 2015a, 2015b). Robot-assisted training showed beneficial effects on motor recovery of upper extremity (Almenara et al., 2015; Cortes et al., 2013; Francisco et al., 2017; Kadivar et al., 2011). More sophisticated technology applications are also used to improve upper extremity function and voluntary motor control. Several groups of researchers reported encouraging results utilizing brain-computer interface controlled functional electrical stimulation for reaching and grasping (Ajiboye et al., 2017; Bouton et al., 2016; Likitlersuang et al., 2018). The majority of these approaches concentrate on the improvement of function by taking advantage of the plasticity of neuronal structures (Ramer, Ramer, & Bradbury, 2014).

The principle of neuroplasticity by first described by Donald Hebb in 1949 (Hebb, 1949), who proposed that structural and metabolic connectivity between two neurons becomes stronger when their activities exhibit a persistent causal relationship with one another. Although popularly summarized by the phrase "cells that fire together wire together", neuroplasticity refers to the dynamic and lasting changes or adaptations of the structure and function of the central nervous system, in response to exogenous or endogenous stimuli, such as changing environment, new information, sensory stimulation, damage, or dysfunction (Piazza & Ibáñez, 2016). Neuroplasticity occurs on a variety of levels. It ranges from physiologic and microscopic changes in a single neuron, such as altered intrinsic excitability, to large-scale functional reorganization of the neural networks (Piazza & Ibáñez, 2016; Wolpaw & Tennissen, 2001). In contrast to the historical view that the spinal cord is a static hardwired structure between brain and periphery, growing evidence indicates that the spinal cord possesses remarkable neuroplastic properties (Christiansen, Lundbye-Jensen, Perez, & Nielsen, 2017; Ding, Kastin, & Pan, 2005).

Functional reorganization of the spinal networks depends on sufficient and appropriate sensory input and concurrent motor training, which is also known as activity-dependent neuroplasticity (Cai et al., 2006; Courtine, van den Brand, Roy, & Edgerton, 2016; Edgerton et al., 2008). Following the injury to the spinal cord, the disconnection of neural pathways between the brain and spinal networks induces various structural and molecular changes that result in a depressed activity state of spinal neurons below the injury site. The absence of critical level of excitability is an essential barrier for activity-dependent plasticity to occur (Edgerton & Roy, 2012). Recent studies indicated that electrical neuromodulation of the spinal cord enables the potential for remodeling of spinal networks and reshaping supraspinal connectivity (Edgerton & Harkema, 2011). The exact mechanism of the electrical spinal cord stimulation remains to be determined; however, tonic activation of dorsal root afferent fibers may facilitate sustainable excitability level of premotor circuitry and also may increase the strength of the synaptic connections of the spared but dormant corticospinal projections. This, in turn, brings interneurons and motor neurons closer to the motor threshold that enables spinal networks to process task-specific sensorimotor information, and also to respond to limited post-injury descending drive for the execution of movement (Courtine, van den Brand, & Musienko, 2011; Gerasimenko, Lu, et al., 2015).

The majority of recent electrical neuromodulation studies have focused on improving locomotor function (Angeli et al., 2018; Darrow et al., 2019; Gill et al., 2018; Grahn et al., 2017; Harkema et al., 2011; Minassian, Hofstoetter, et al., 2016; Wagner et al., 2018). These studies targeted the central pattern generator (CPG) located in lumbosacral spinal cord that has automaticity for the basic rhythm and timing of stepping and independent standing in the absence of supraspinal influences (AuYong & Lu, 2014; Dietz, Muller, & Colombo, 2002; Grau, 2014; Grau, Barstow, & Joynes, 1998; Harkema, 2008; Lacquaniti, Ivanenko, & Zago, 2012; Young, 2015). In contrast to the automaticity of the CPG to some degree for controlling locomotor function, neuronal pathways for upper extremity motor control are more intricate due to neuromechanical complexity of the precise hand movements (Perez, 2015; Pierrot-Deseilligny, Burke, & Burke, 2012; Rossi-Durand, Jones, Adams, & Bawa, 1999; Sabbahi & Khalil, 1990). Only a few studies addressed the effect of electrical neuromodulation of the cervical spinal cord for the restoration of upper extremity function (Dimitrijevic M. M. et al., 1986; Dimitrijevic, Illis, Nakajima, Sharkey, & Sherwood, 1986; Gad, Lee, et al., 2018; D. C. Lu et al., 2016; Waltz, Andreesen, & Hunt, 1987). Restoration of upper extremity function remains an important clinical goal (Trumbower, 2018) given the paramount importance for people with tetraplegia. Even partial recovery of hand and arm function could dramatically improve the independence and quality of life for people with tetraplegia (French et al., 2010).

1.2 Aim and objectives

The overall aim of this dissertation was to evaluate the therapeutic potential of transcutaneous spinal cord stimulation to enhance upper extremity function in chronic SCI. We hypothesized that non-invasive electrical spinal cord stimulation applied to the cervical spinal cord enables volitional motor control of the upper extremity muscles and promotes long-term restoration of hand and arm function in both motor complete and incomplete tetraplegia. To test our hypothesis, we used a combination of transcutaneous cervical spinal stimulation and intensive functional task training to mimic the most likely application of this technology in the clinic. We quantified immediate functional improvements of the hand and arm during the application of stimulation and also documented long-term benefits that persist beyond the stimulation. We directly compared improvements that were achieved by intensive functional task training alone to those obtained when electrical spinal cord stimulation was paired with training.

1.3 Overview of the dissertation

This dissertation is divided into five chapters. Chapter 2 is a literature review of electrical spinal cord stimulation as an emerging therapeutic tool for restoration of function after spinal cord injury. The early findings in experimental animal studies and translation of these findings to human studies are discussed.

Chapter 3 presents the results of our pilot study. In this case study, the non-invasive application of electrical spinal cord stimulation demonstrated promising potential to restore prolonged hand and arm function in an individual with incomplete chronic tetraplegia.

Chapter 4 includes the findings from transcutaneous spinal cord stimulation paired with intensive functional task training for six additional participants with cervical SCI. In this study, we showed that combining electrical neuromodulation of the spinal cord with intensive task training rapidly improved volitional motor control both in chronic motor complete and incomplete SCI while the stimulator was active. Additionally, gains were sustained three to six months without stimulation or training, suggesting that electrical stimulation can promote neuroplasticity in spinal networks and promote lasting recovery after SCI.

Finally, Chapter 5 summarizes overall findings and the contribution of this dissertation with concluding remarks and discusses the directions for future work.

Chapter 2 Therapeutic electrical spinal cord stimulation in spinal cord injury: A literature review

2.1 Abstract

Therapeutic electrical spinal stimulation is an emerging neuromodulation strategy in spinal cord injury treatment. Experimental studies in animal models provided strong evidence that electrical stimulation of the spinal cord restores motor control and improves function in paralyzed muscles. In the light of these findings, electrical spinal cord stimulation began translation into human studies. The majority of the human studies were focused on the therapeutic potential of epidural stimulation on locomotor function. While impressive gains occur with invasive epidural stimulation, a novel non-invasive spinal stimulation strategy has emerged over the past few years. By adopting a 10 kHz carrier-frequency, this method permits delivery of high intensity electrical currents over the skin without causing discomfort. The results of recent studies show that non-invasive stimulation may lead to similar improvements with the advantage of not requiring surgery.

2.2 Introduction

Spinal cord injury has been postulated untreatable since ancient times. Fueled by the growing evidence of spinal cord neuroplasticity and rapidly developing neural engineering field, this belief began to change during the last few decades. Newer neurorestorative therapies are emerging based on the huge body of experimental studies. Among these, electrical spinal cord stimulation is one of the most promising neuromodulation strategies to restore functions in spinal cord injury (SCI) (Moritz, 2018).

Functional outcomes and clinical presentation of SCI are heterogeneous depending on the level, extent, and severity of the damage. Neurophysiological evaluations in patients with clinically complete SCI and post-mortem human and animal studies indicate the evidence of spared sensory and motor connections across the lesion in more than 80 % of the cases (Dimitrijevic, 1988; Kakulas, 1999; McKay, Lim, Priebe, Stokic, & Sherwood, 2004; Sherwood, Dimitrijevic, & McKay, 1992). Dimitrijevic et al. (1988) coined the term “discomplete” to describe these neurophysiologically incomplete lesions. Indeed, even in clinically complete SCI, absolute deprivation of supraspinal influence is rare. However, most of the intact neural structures, including spared connections between the brain and the spinal cord, and also spinal circuits below the injury site are functionally silent with a reduced state of excitability. The significance of discomplete lesions is that voluntary motor control can be promoted via augmenting these operational neural pathways. In other words, given that both supraspinal and spinal plasticity are critical for motor learning, neuromodulation of these intact but dormant neural structures can be used to facilitate neuroplasticity and consequently enhance voluntary motor control after SCI (Courtine et al., 2011; Mayr, Krenn, & Dimitrijevic, 2016).

After Sherrington’s observations that revealed the significance of peripheral inputs on spinal motor outputs in spinal transected cats and dogs (Sherrington, 1910), neural control of movement and various neuromodulation strategies have been investigated intensively to enable motor control following SCI. Therapeutic neuromodulation is defined as the alteration of nerve activity through targeted delivery of a stimulus, such as intensive task-specific training, electrical stimulation, or chemical agents, to attain desired physiologic responses (Dolbow et al., 2015; James, McMahon, Field-Fote, & Bradbury, 2018).

De Leon and co-workers studied the effect of weight-bearing training to improve walking and standing in spinally transected cats (De Leon, Hodgson, Roy, & Edgerton, 1998). They showed that repetitive stimulation of certain sensory and motor pathways via task-specific training encodes and strengthens these synapses to perform practiced movement successfully. Task-specific neuromodulation strategy showed successful results in humans with incomplete SCI, as well. Several groups reported up to 92% of research participants with incomplete SCI achieved functional walking ability following body weight supported locomotor training (Barbeau, Ladouceur, Norman, Pepin, & Leroux, 1999; Behrman & Harkema, 2000; Dobkin et al., 2007; Wernig & Muller, 1992). However, individuals with motor complete injuries did not benefit from the same training to the same extent (Dietz, 2009). This failure is attributed to the absence of some critical level of excitability of the spinal neurons in severe SCI (Edgerton & Roy, 2012), and triggered the development of new strategies to overcome depressed state of spinal neuronal networks.

The beneficial effect of electrical spinal cord stimulation on voluntary motor control drew attention for the first time in the 1970s (Cook & Weinstein, 1973). Authors reported motor improvement in their patient with multiple sclerosis who was treated with electrical stimulation for pain. The next studies with dorsal column stimulation showed improvements in bladder function, reduced spasticity and increased endurance in patients with various neurologic disorders (Dooley & Nisonson, 1981; Illis, Oygar, Sedgwick, & Awadalla, 1976; Siegfried et al., 1978).

Based on the recent advances in neuroscience and engineered biodevices, a new generation of neurorehabilitation interventions are developing. These approaches demonstrate quite encouraging results to create long-term changes in neural circuits.

2.3. Animal studies with electrical spinal cord stimulation

In animal spinal injury models, various procedures of electrical spinal stimulation were studied (Table 2.1). These procedures include dorsal root, intraspinal, epidural, and transcutaneous electrical stimulation Electrophysiologic and functional responses of hindlimb stepping and forelimb reaching movements obtained by electrical stimulation of different segmental levels showed exciting potential for motor recovery in cats, rats, and non-human primates (Table 2.1).

Different stimulation parameters, such as sub- and suprathreshold intensities were tested in animal studies to identify the neural targets of stimulation and to evaluate the possible mechanisms of neuromodulation (Capogrosso et al., 2016; Ichiyama, Gerasimenko, Zhong, Roy, & Edgerton, 2005; Iwahara, Atsuta, Garcia-Rill, & Skinner, 1992; Ranck, 1975). Particular patterns of motor responses to specific localization of electrical spinal stimulation were also determined to optimize functional outcomes. For example, sacral stimulation primarily facilitated extensor muscle contractions; lumbar stimulation facilitated flexor muscle contractions, and combination of two locations showed synergistic facilitation of both muscle groups during standing and stepping in spinal rats (Courtine et al., 2009).

Table 2.1 Animal studies to restore motor function via electrical spinal cord stimulation

Species	Stimulation type	Reference
Hindlimb (Locomotion)		
Cat	Epidural and subdural	(Iwahara et al., 1992)
Cat	Intraspinal microstimulation	(Dalrymple, Everaert, Hu, & Mushahwar, 2018; Holinski et al., 2016; Mushahwar, Gillard, Gauthier, & Prochazka, 2002)
Rat	Epidural	(Gad et al., 2013; Ichiyama et al., 2005; Shah et al., 2016)
Rat	Epidural (electrochemical)	(van den Brand et al., 2012)
Non-human primates	Epidural + BCI	(Capogrosso et al., 2016)
Forelimb (Reaching)		
Rat	Epidural	(Alam et al., 2017)
Rat	Intraspinal microstimulation	(Kasten, Sunshine, Secrist, Horner, & Moritz, 2013; Sunshine et al., 2013)
Rat	dc transcutaneous + motor cortex	(Yang et al., 2019; Zareen et al., 2017)
Non-human primates	Intraspinal microstimulation	(Moritz, Lucas, Perlmutter, & Fetz, 2007)
Non-human primates	Intraspinal microstimulation + BCI	(Zimmermann, Seki, & Jackson, 2011)

BCI: brain computer interface, dc: direct current

Two groups reported the beneficial effect of spinal stimulation on the autonomic nervous system in animal models. The authors reported improved bladder function in cats and rats (Desautels et al., 2015; Gad et al., 2014). Additionally, several groups used combination therapies to investigate the synergistic interactions of electrical spinal cord stimulation and pharmacological agents. Several serotonin receptor agonists showed promising results for such combination therapies in animal models and can be used to facilitate or optimize the recovery of motor function (Courtine et al., 2009; Gerasimenko et al., 2007; Ichiyama et al., 2008; Lyalka et al., 2011).

Overall, animal studies provided strong evidence that electrical stimulation of the spinal cord modifies dysregulated sensorimotor functions and enables volitional motor control after SCI. Based on the assuring findings from animal studies and advances in material science and electrical and computer engineering, electrical spinal cord stimulation began translation into clinical studies.

2.4 Human studies with epidural spinal cord stimulation

Clinical use of electrical spinal cord stimulation emerged as a therapeutic tool for the management of intractable pain. It was first used in a patient with metastatic cancer in 1967 (Shealy, Mortimer, & Reswick, 1967). Since then, besides utilization widely for neuropathic and vascular originated pain treatment, the effect of epidural stimulation was investigated on various motor disorders, such as multiple sclerosis, cerebral palsy, dystonia, torticollis, spinocerebellar degeneration and traumatic brain injury (Cook & Weinstein, 1973; Illis et al., 1976; Waltz, 1982; Waltz et al., 1987; Waltz, Reynolds, & Riklan, 1981). In these studies, epidural spinal stimulation was shown effective in reduction of spasticity (Cook, Taylor, & Nidzgorski, 1981; Davis, Gray, & Kudzma, 1981; Read, Matthews, & Higson, 1980; Reynolds & Oakley, 1982; Siegfried et al., 1978), improvement of bladder function (Berg et al., 1982; Cook et al., 1981; Read et al., 1980) and alleviation of ataxia (Cook et al., 1981; Davis et al., 1981). However, surgery and hardware malfunction complication rates were relatively high, and many patients required correction surgery or removal of the implanted system (Sherwood, Sharkey, & Dimitrijevic, 1980; Waltz, 1997). Meanwhile, the stimulator evolved from a simple 2-electrode array to contemporary, sophisticated systems. Current multielectrode computerized systems have newer designs of electrodes with multiple active contacts that allow controlling the electrical field more precisely, their power capacity is increased and combined with compact electronic controls that offer a wide range of stimulation parameters (Dmochowski, Datta, Bikson, Su, & Parra, 2011).

2.4.1 Epidural spinal cord stimulation for restoration of locomotor function after SCI

Early studies on SCI demonstrated beneficial effects of epidural spinal cord stimulation on spasticity management (Barolat-Romana, Myklebust, Hemmy, Myklebust, & Wenninger, 1985; Dimitrijevic M. M. et al., 1986; Dimitrijevic M. R. et al., 1986). One of these studies evaluated the effect of the clinical outcomes of spasticity in participants with cervical and thoracic level injuries (Dimitrijevic M. M. et al., 1986). Spasticity was reduced in 63% of the cases, while stimulation was found more effective in incomplete lesions and when stimulated below the injury level in this study. The same group of authors also investigated the neurophysiologic responses to epidural spinal stimulation in their participants who positively responded to epidural stimulation during their clinical study (Dimitrijevic M. R. et al., 1986). The results of this study indicated that higher stimulation intensities enhance spasticity; however, segmental reflexes could be modified by the adjustment of stimulation intensity. They also noted that the effects were selective, depending on the spared segmental networks and neural pathways.

The majority of the research that evaluates the effect of epidural spinal cord stimulation on restoring motor control is focused on locomotor function. The first case study on a participant with C5 incomplete injury revealed that continuous epidural stimulation delivered to the lumbar spinal cord enabled voluntary contraction of the left quadriceps muscle. Voluntary contraction was strong enough to completely extend the knee against gravity when sitting. Before stimulation, this muscle was completely paralyzed, and volitional control was obtained only when the stimulator was active (Barolat, Myklebust, & Wenninger, 1986).

In a case series of five participants with cervical and thoracic level, AIS A and B category injury, researchers implanted epidural electrodes to low thoracic vertebra level and observed strong hip and knee extension in supine position when stimulation was ongoing (Jilge, Minassian, Rattay, Pinter, et al., 2004). The authors suggested that epidural stimulation at a low thoracic level can initiate and retain an extension pattern generator organization and can be used for standing after complete injuries. Furthermore, lumbosacral epidural stimulation has been shown to elicit rhythmic and locomotor-like lower extremity activity in three studies, including a total of 26 motor complete SCI individuals (Danner et al., 2015; Dimitrijevic, Gerasimenko, & Pinter, 1998; Minassian et al., 2004).

Carhart and co-workers (Carhart, He, Herman, D'Luzansky, & Willis, 2004) combined task-specific locomotor training with epidural stimulation. In this case study, the participant had a C5-C6 level, AIS C incomplete injury, and was wheelchair-dependent at the time of admission. Partial weight-bearing therapy on the treadmill did not improve his overground locomotor function. Combined with epidural stimulation between T10-12 vertebral levels, this participant was able to walk over ground with a front wheeled-walker in home and community settings, his perceived exertion rate improved, walking speed and endurance increased at the end of four-months treatment. The results of this study suggested for the first time that electrical spinal cord stimulation facilitates motor recovery via augmentation of use-dependent neuroplasticity.

Based on the improved understanding of use-dependent plasticity and growing evidence that indicates electrical stimulation can leverage the intrinsic capacity of neural plasticity, SCI research gained momentum during the last decade (Ramer et al., 2014). In two successive reports, Harkema and co-workers presented exciting results using lumbosacral epidural stimulation combined with intensive locomotor training (Angeli, Edgerton, Gerasimenko, & Harkema, 2014; Harkema et al., 2011). Before the implantation of epidural stimulator, four young adult male participants with motor complete SCI between C5 and T4 level involved in intensive locomotor training up to 9 weeks without showing an improvement in their locomotor function. Following epidural stimulation, all participants gained voluntary leg movements and independent weight-bearing standing. The authors concluded that epidural stimulation promotes the development of functional connectivity across the lesion. They also emphasized that lumbosacral spinal networks are capable of learning with task-specific training and improving motor pool recruitment to promote force generation and accuracy.

Another group successfully replicated these results. Grahn and coworkers (Grahn et al., 2017) confirmed all of the findings presented by the Harkema group in a single case study. In addition, they showed that their 26 years old male participant with T6, AIS A SCI regained voluntary control of step-like movements and rhythmic muscle activity in the vertical position with partial body-weight support within the two-weeks of stimulation.

Both groups of researchers continued their experimental treatments of lumbosacral epidural stimulation and intensive training with these participants. Following 15 to 85 weeks of continuous treatment, two of the four participants with cervical and thoracic level AIS B category injuries progressed to overground walking with assistive devices (Angeli et al., 2018). The other two participants with AIS A category injury achieved independent standing, trunk stability, and body weight supported stepping on the treadmill. Another observation on one of these participants provided evidence that epidural stimulation enabled long-term plasticity (Rejc, Angeli, Atkinson, & Harkema, 2017). Progressive recovery of volitional leg movement and standing persisted without stimulation in that participant who had C7 AIS B SCI. This finding suggested that neural adaptations in the spinal cord via electrical neuromodulation enable recovery from complete paralysis to refine volitional motor control. Gill and co-workers reported similar results (Gill et al., 2018). Their participant with T6 AIS A SCI was able to perform independent treadmill stepping without assistance or the bodyweight support and achieved overground walking with a front-wheeled walker, as well, by the end of 43 weeks.

In a more recent report, Darrow and co-workers contributed to the generalizability of the previous findings (Darrow et al., 2019). In this study, two female participants with T4 and T8 level, AIS A category injury enrolled in the study, at the age of 48 and 52 years, 5- and 10-years post-injury. Both participants immediately regained volitional motor control in their lower extremities when the stimulator was on, without pre-implantation intensive locomotor training.

Epidural spinal cord stimulation studies utilized an open-loop, continuous stimulation to enable functional restoration. A short while ago, a new stimulation strategy was introduced by a multidisciplinary group of researchers (Wagner et al., 2018). They developed a closed-loop system that integrated an implanted pulse generator with real-time, voice-controlled triggering capabilities and an inertial measurement unit that detects the intended movement. This system allowed to control the delivery of spatially selective stimulation to the lumbosacral spinal cord with timing that coincided with the intended movement. Utilizing this targeted neurotechnology, researchers suggested that efficacy of real-time, intended movement triggered epidural spinal cord stimulation is superior to open-loop continuous stimulation. Three participants who had SCI between C4 and C8 level and AIS category C and D treated with this new strategy achieved adaptive control of paralyzed muscles during overground walking within one week, when the stimulator was activated. After a few months of rehabilitation coupled with the closed-loop stimulation system, participants regained volitional control of paralyzed muscles without stimulation. Additionally, the closed-loop spatiotemporal stimulation enabled walking and cycling in community settings.

2.4.2 Epidural spinal cord stimulation for restoration of hand and arm function after SCI

Even though upper limb dysfunction is the most devastating consequence of the cervical SCI and the people with tetraplegia consistently prioritize regaining hand and arm function, to date, only a few studies have addressed the utilization of epidural stimulation for restoration of upper limb function. However, almost three decades ago, Waltz and co-workers portrayed the beneficial effects of electrical spinal cord stimulation on upper limb function (Waltz et al., 1987). In this study, 78% of the 112 patients with tetraplegia improved in their upper extremity motor function, spasticity, spasms, pain, and bladder control. Although clinical features of the patients and treatment protocols were not stated in detail, this report provides significant information about the promising potential of electrical cervical cord stimulation for the restoration upper limb function. As a separate note, the authors pointed out that improvements in muscle tone and motor function enabled to resume rehabilitation program in many cases, otherwise not possible or effective.

Recently, Lu and co-workers investigated the effects of cervical epidural stimulation on volitional hand strength and control (Lu D. C. et al., 2016). Two participants with chronic, C5 and C6 level, AIS B category cervical SCI enrolled in the study when epidural stimulators were implanted for treatment of refractory pain. Epidural implants with 16-contact electrodes were placed over the C4-T1 level. Stimulation parameters consisted of amplitudes ranged between 0.1 and 10.0 mA, frequencies ranged between 2 and 40 Hz, and the pulse width was at 210 μs. Handgrip forces were measured repeatedly at the pre-implantation phase. One of the participants was trained and tested for handgrip performance weekly after implantation for eight weeks, and the other participant 7 times daily, before, during, and after stimulation. The results showed a cumulative increase of handgrip forces approximately 2- to 3-fold compared to baseline in both subjects when the stimulator was active, and the force generation was largely maintained when the stimulator turned off at the end of the session.

2.4.3 Effect of epidural spinal cord stimulation beyond motor function in SCI

During treatment with epidural spinal cord stimulation, remarkable improvements were attained on autonomic system functions, as well. Effects of epidural stimulation on cardiovascular functions included modulation of arterial blood pressure and improvement in orthostatic intolerance during tilt challenge in participants who had existent cardiovascular dysfunction at the beginning of the study (Aslan et al., 2018; Darrow et al., 2019; Harkema, Legg Ditterline, et al., 2018; Harkema, Wang, et al., 2018). In these studies, the authors emphasized the importance of individualized and specific settings of stimulation that were different from stimulation parameters used for the restoration of motor function.

Improvements in bladder functions due to application of epidural stimulation included regained volitional voiding with minimum residual volume or improved reflexive voiding efficiency, and restored bowel-bladder synergy (Darrow et al., 2019; Harkema et al., 2011; Herrity, Williams, Angeli, Harkema, & Hubscher, 2018). Moreover, restoration of sexual functions in one male and one female participant were noted (Darrow et al., 2019; Harkema et al., 2011). Temperature regulation was another beneficial effect of epidural stimulation that was experienced by another research participant (Harkema et al., 2011). All participants included in these reports were in the chronic stage of motor complete SCI.

In aggregate, findings reported by multiple independent groups revealed that epidural spinal cord stimulation is one of the most promising neuromodulation strategies in SCI. However, it is an invasive intervention and requires intensive training of clinicians for cost-effective utilization of this emerging high-tech procedure. Furthermore, experience gained from its application for pain treatment now more than 40 years indicates that complication rates related to surgery or device malfunction are considerable (Mekhail et al., 2011). For that reason, non-invasive approaches to stimulate the spinal cord may be an alternative strategy to facilitate its widespread use.

2.5 Human studies with transcutaneous spinal cord stimulation

Commercially available direct current stimulators were used to activate the posterior spinal cord roots non-invasively (Cogiamanian et al., 2012; Cogiamanian, Vergari, Pulecchi, Marceglia, & Priori, 2008; Minassian et al., 2007). Neurophysiological and computer modeling studies indicated that this noninvasive technique activates the same neural structures in the spinal cord and evokes similar responses as epidural stimulation (Capogrosso et al., 2013; Danner, Hofstoetter, Ladenbauer, Rattay, & Minassian, 2011; Hofstoetter, Freundl, Binder, & Minassian, 2018; Milosevic, Masugi, Sasaki, Sayenko, & Nakazawa, 2019).

The Minassian and Hofstoetter group used this type of transcutaneous direct current stimulation and reported reduced spasticity and increased activity of lumbosacral central pattern generators in individuals with both incomplete (Hofstoetter et al., 2015; Hofstoetter et al., 2014) and motor complete SCI (Minassian & Hofstoetter, 2016; Minassian, McKay, Binder, & Hofstoetter, 2016). Comparable results were achieved between transcutaneous and epidural stimulation (Hofstoetter et al., 2018).

Over the past few years, a novel non-invasive spinal cord stimulation strategy has emerged by adopting the high carrier-frequency waveforms. This new strategy utilizes a unique waveform of biphasic or monophasic, rectangular, 1 ms pulses that are delivered at a frequency of 30 Hz. Each pulse is filled with an overlapping frequency of 10 kHz, which permits high stimulation intensities to pass through the skin and reach the spinal cord without causing discomfort (Gerasimenko, Gorodnichev, Moshonkina, et al., 2015). Application of this type of stimulation to thoracolumbar spinal cord activated reciprocal alternating patterns of coordinated stepping movements in healthy subjects (Gerasimenko, Gorodnichev, Moshonkina, et al., 2015; Gerasimenko, Gorodnichev, Puhov, et al., 2015). In patients with complete SCI, transcutaneous spinal cord stimulation improved lower extremity function in gravity neutral position and facilitated stepping assisted by an exoskeleton (Gad et al., 2017; Gad, Gerasimenko, et al., 2015). Additionally, similar to epidural stimulation, transcutaneous spinal cord stimulation normalized bladder and urethral sphincter function, reduced detrusor overactivity, decreased detrusor-sphincter dyssynergia, increased bladder capacity and enabled voiding in patients with cervical and thoracic SCI (Gad, Kreydin , Zhong, Latack, & Edgerton, 2018). This non-invasive spinal cord stimulation also improved trunk control, sitting posture and balance following cervical and thoracic SCI (Rath et al., 2018).

Preliminary evidence utilizing newly developed transcutaneous electrical spinal cord stimulation strategy is showing exciting potential to restore of UE function effectively and non-invasively. Gad and co-workers studied handgrip force improvements in 6 AIS B and AIS C chronic cervical SCI subjects (Gad, Lee, et al., 2018). They reported that only after eight sessions with this new transcutaneous stimulation strategy, maximum voluntary handgrip forces increased by

~3-fold in the presence of stimulation and ~2-fold without simultaneous stimulation. Our pilot case study subject who had C3 level chronic central cord injury improved substantially in terms of motor and sensory function (Inanici et al., 2018). Following four weeks of combined stimulation and sensorimotor training, the Graded Redefined Assessment of Strength, Sensation, and Prehension test score increased 52 points, and the upper extremity motor score improved 10 points. Pinch strength increased 2- to 7-fold in the left and right hands, respectively. Sensation recovered on trunk dermatomes, and overall neurologic level of injury improved from C3 to C4. The subject began partial self-feeding at home in the second week of the intervention for the first time since his injury and continued this activity even after the intervention. Most notably, functional gains persisted for over three-month follow-up without further treatment. These data suggest that non-invasive electrical stimulation of spinal networks can promote neuroplasticity and long-term recovery following spinal cord injury.

More recently, the synergistic treatment effect of transcutaneous spinal cord stimulation and monoaminergic agonist buspirone on the upper limb function is investigated (Freyvert et al., 2018). Six chronic motor complete participants with cervical injuries at C5 or a higher level were tested for handgrip function, EMG responses hand function test, and upper extremity motor score. Results indicated that all measured outcomes improved progressively during alternating use of buspirone and placebo coupled with transcutaneous cervical cord stimulation. Gains were partly sustained 3-months after treatment. The authors concluded that this combinatory treatment resulted in significant improvement of upper limb function, without providing information about the independent effect of each intervention.

To summarize, non-invasive spinal cord stimulation is a highly promising intervention for the restoration of motor functions for both upper and lower limb treatment in people with SCI. The findings obtained from multiple studies indicate that its effect is comparable to epidural stimulation, with the significant advantage of not requiring surgery.

2.6 Current understanding of the mechanism of action driven by electrical spinal cord stimulation

The mechanism by which electrical spinal cord stimulation improves motor function is largely unknown. Recent proof-of-concept studies suggest that both epidural and transcutaneous stimulation have similar neuromodulatory effects (Hofstoetter et al., 2018). Neural targets of electrical stimulation depend on the stimulation approach, electrode position, and the stimulation parameters. In the view of electrophysiologic studies and computational modeling, several pieces of mechanism are identified (Capogrosso et al., 2013). Intraspinal microstimulation directly activates spinal motor neurons and interneuron circuits (Kasten et al., 2013). Distinct stimulation frequency ranges evoke distinct muscle responses in complete SCI individuals. For example, 20-50 Hz frequencies over the lumbosacral region elicit rhythmic step like-movements, and 5-15 Hz frequencies result in continuous contractions in the target muscles, such as sustained extension. Frequency-dependent activation is attributed to the differential responsiveness of intact but depressed spinal pathways (Jilge, Minassian, Rattay, & Dimitrijevic, 2004). Another interesting finding from the electrophysiologic studies is that EMG recordings from spinal cord stimulation induced muscles show single compound motor unit potentials. This finding suggests that there is monosynaptic interaction between spinal cord stimulation induced afferent volleys, interneuronal structures, and corresponding motor nuclei (Jilge, Minassian, Rattay, & Dimitrijevic, 2004).

The effect of electrical spinal cord stimulation on molecular level remains to be determined. In healthy CNS, glutamate is the major excitatory neurotransmitter and glutamatergic reticulospinal neurons provide the tonic excitatory drive to engage spinal locomotor networks (Hagglund, Borgius, Dougherty, & Kiehn, 2010). The injured spinal cord is deprived of this tonic excitatory drive. Tonic electrical stimulation modifies the overall physiological state of the locomotor circuitry via strengthening synaptic connections and reinforcing specific circuitry, and it is suggested that electrical spinal stimulation substitutes or simulates reticulospinal tonic drive (Courtine et al., 2016).

Current understanding is that electrical stimulation activates the spinal cord predominantly via recruiting large-to-medium diameter proprioceptive and cutaneous afferents to provide sub-threshold excitation to the interneurons and motor neurons within the spinal cord caudal to the lesion (Hofstoetter et al., 2018; Milosevic et al., 2019). Motor neurons closer to threshold are then more easily activated by remaining descending pathways from the brain, restoring volitional control of movement (Edgerton & Roy, 2012; Sayenko, Angeli, Harkema, Edgerton, & Gerasimenko, 2014).

Chapter 3 A case study on transcutaneous electrical spinal stimulation to promote recovery of upper extremity function in chronic spinal cord injury

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"©2018 IEEE. Reprinted, with permission, from [Inanici, F., Samejima, S., Gad, P., Edgerton, V. R., Hofstetter, C. P., & Moritz, C. T. (2018). Transcutaneous Electrical Spinal Stimulation Promotes Long-Term Recovery of Upper Extremity Function in Chronic Tetraplegia. IEEE Trans Neural Syst Rehabil Eng, 26(6), 1272-1278. doi:10.1109/tnsre.2018.2834339]."

3.1 Abstract

Upper extremity function is the highest priority of tetraplegics for improving quality of life. We aim to determine the therapeutic potential of transcutaneous electrical spinal cord stimulation for restoration of upper extremity function. We tested the hypothesis that cervical stimulation can facilitate neuroplasticity that results in long-lasting improvement in motor control. A 62-year-old male with C3, incomplete, chronic spinal cord injury participated in the study. The intervention comprised three alternating periods: (1) transcutaneous spinal stimulation combined with physical therapy, (2) identical physical therapy only, and (3) a brief combination of stimulation and physical therapy once again. Following four weeks of combined stimulation and sensory motor training, all of the following outcome measurements improved: The Graded Redefined Assessment of Strength, Sensation and Prehension test score increased 52 points and upper extremity motor score improved 10 points. Pinch strength increased 2- to 7-fold in left and right hands, respectively.

Sensation recovered on trunk dermatomes, and overall neurologic level of injury improved from C3 to C4. Most notably, functional gains persisted for over three-month follow-up without further treatment. These data suggest that non-invasive electrical stimulation of spinal networks can promote neuroplasticity and long-term recovery following spinal cord injury.

Index Terms — neuroplasticity, spinal cord injury, transcutaneous electrical spinal cord stimulation, upper extremity function

3.2 Introduction

Traumatic spinal cord injury (SCI) affects the cervical spine in 58% of cases (NSCISC, 2016). Ensuing paralysis of the hand and arm imposes significant limitations in most activities of daily living and impairs quality of life. Patients have difficulties feeding, grooming, handwriting or performing other upper extremity motor tasks. In these individuals, restoration of hand and arm function is the highest treatment priority, five times greater than bladder, bowel, sexual or lower extremity dysfunction (Anderson, 2004).

Given the limited regeneration potential of the spinal cord, reorganization of spared spinal circuits and facilitation of weak or silent descending drive are important targets for restoration of sensory and motor function after SCI. Growing evidence indicates that tonic electrical spinal stimulation can leverage the intrinsic capacity of neural plasticity, and can be utilized for restoration of function after SCI (Dietz & Fouad, 2014; Ievins & Moritz, 2017). Epidural stimulation can enhance conscious motor control of locomotion in humans with incomplete SCI (Barolat et al., 1986; Carhart et al., 2004; Sherwood et al., 1980), and produce initiation of voluntary leg movements and gains in postural control even in cases of clinically-complete SCI (Angeli et al., 2014; Grahn et al., 2017; Harkema et al., 2011). In addition, direct current spinal cord stimulation via commercially available stimulators was used to activate the posterior spinal cord roots through the skin (Cogiamanian et al., 2012). Minassian and colleagues reported reduced spasticity and increased activity of lumbosacral central pattern generators in both incomplete (Hofstoetter et al., 2015) and motor complete (Minassian, Hofstoetter, et al., 2016) individuals following spinal cord injury.

Although recent studies of spinal cord stimulation have largely focused on lower extremity function, almost three decades ago Waltz et al. reported improvement in upper extremity motor function, reduced spasticity and improved bladder function in 65% of the 169 patients with SCI treated with cervical epidural stimulation (Waltz et al., 1987). Recently, Lu et al. demonstrated that even seven or eight sessions of cervical epidural stimulation improved hand motor function in two human subjects with chronic, motor complete cervical SCI (Lu D. C. et al., 2016).

Transcutaneous electrical spinal cord stimulation is a novel, non-invasive strategy to stimulate the spinal cord from the surface of the skin. Utilization of a unique waveform permits high-current electrical stimulation to reach spinal networks without causing discomfort (Gerasimenko, Gorodnichev, Moshonkina, et al., 2015). Application of this type of stimulation to lumbosacral spinal cord improved lower extremity function for several people with spinal cord injury (Gad et al., 2017; Gerasimenko, Lu, et al., 2015). Recently, Gad et al. reported that after 8 sessions of transcutaneous stimulation, maximum voluntary hand grip forces increased by ~3-fold in the presence of stimulation and ~2-fold without simultaneous stimulation in 6 AIS B and AIS C chronic cervical SCI subjects (Gad, Lee, et al., 2018). The present case study was designed to test the therapeutic potential of transcutaneous spinal cord stimulation on long-term restoration of upper extremity function. We tested the hypothesis that the combination of cervical transcutaneous spinal cord stimulation combined with intensive physical therapy (PT) can modulate spinal networks to create lasting improvements in hand and arm function in chronic, incomplete SCI.

3.3 Methods

3.3.1 Clinical Characteristics of the Subject

A 62-year-old male with cervical SCI participated in the study. Two years prior to beginning the study, this man sustained an incomplete cervical SCI while body surfing. The injury was graded as American Spinal Injury Association (ASIA) Impairment Scale (AIS) (Kirshblum et al., 2011) category D (C3 AIS D). Acute magnetic resonance imaging of the cervical spine revealed hemorrhage and contusion of the spinal cord at C3/4 in the setting of severe spinal stenosis. Cervical x-rays and CT imaging was obtained in order to rule out bony fracture or instability. The patient was initially treated conservatively. Following modest initial functional recovery, progress came to a halt and repeat cervical MRI four months after injury revealed spinal myelomalacia at C3/4 in the setting of severe cervical spinal stenosis (Fig. 3.1A). Six months following his injury, he underwent a C3-7 laminectomy and arthrodesis (Fig. 3.1B).

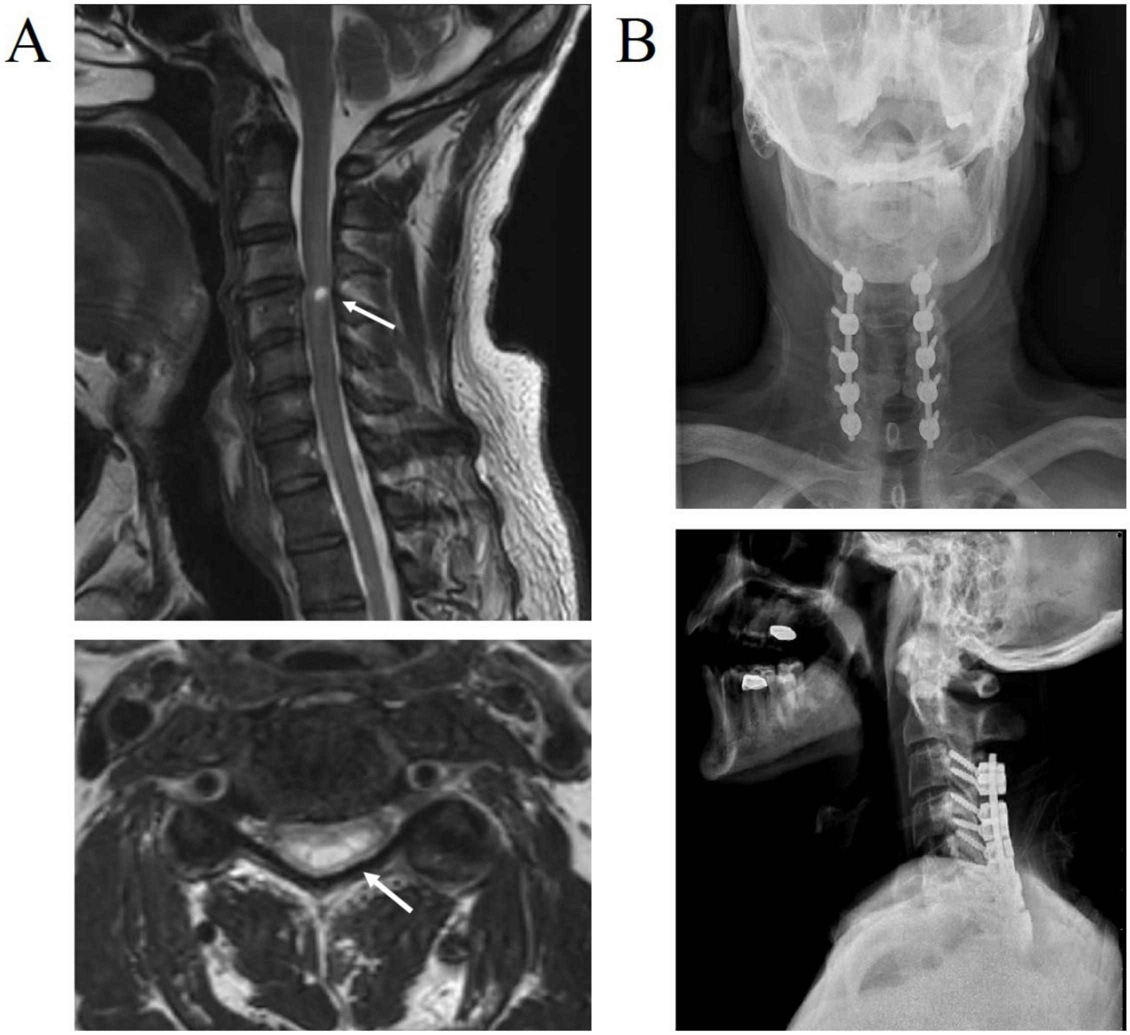


Figure 3.1 Radiographic images of the injury location and decompression surgeryof the cervical spine. (A) T2 weighted sagittal (top) and axial (bottom) magnetic resonance images of the subject's cervical spine at 6 months post-injury. Arrows shows high intensity T2 signal of myelomalacia and atrophy at C3 and C4 spinal level. (B) Anteroposterior (top) and lateral (bottom) x-ray images of cervical vertebra showing laminectomy and arthrodesis surgery

He participated in standard inpatient physical rehabilitation for six months that included occupational therapy and gait training. At discharge, his neurological level of injury and AIS category did not change. Despite adequate muscle strength in both lower and left upper extremities, he was completely dependent for all self-care activities (feeding, bathing, dressing, grooming, bowel and bladder management), and had limited indoor walking with moderate assistance for transfers, standing, balance and stepping. After discharge, he attended an exercise-based therapy center regularly, approximately 2 hours per day, 4-5 times per week until the time of this study. He also participated in lower extremity exercise therapy at home on a regular basis using an elliptical trainer.

3.3.2 Procedures

This study is registered with ClinicalTrials.gov, number NCT03184792. The subject signed informed consent for all procedures, which were approved by University of Washington Institutional Review Board. The study consisted of two weeks baseline measurements, nine weeks alternating intervention program and three months follow-up testing with no further therapy.

Baseline evaluation consisted of full physical and neurological examinations including the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) assessment. Upper extremity functional capacity and performance were evaluated by the Graded Redefined Assessment of Strength, Sensibility and Prehension (GRASSP) test (Kalsi-Ryan, 2014) as the primary outcome measure. Lateral pinch strength was also measured (Jamar Hydraulic Pinch Gauge, Lafayette Instruments, USA). Prior to beginning treatment, the GRASSP test and strength measurements were repeated three times over two weeks to explore the consistency of functional status and to document possible learning effects of the tests. WHO

Quality of Life – BREF (Skevington, Lotfy, & O'Connell, 2004), SF-Qualiveen (Bonniaud, Bryant, Parratte, & Guyatt, 2008) and the Spinal Cord Independence Measure III (SCIM III) (Bluvshtein et al., 2011) questionnaires were used to address quality of life and subject's ability to perform activities of daily living.

A three-phase, alternating intervention program delivered: (1) Transcutaneous electrical spinal cord stimulation accompanied by activity-based physical therapy (PT) targeting upper extremity functions for the first four weeks, (2) PT only for the next four weeks, and (3) stimulation + PT again for one week. This order of interventions was derived from a randomized two arm cross over design. Participants are randomly assigned to either PT only or stimulation + PT intervention phases (AB or BA). This subject randomized into stimulation + PT intervention first. The rationale for this study design is to control for the after-effect of either PT only and/or stimulation + PT. As the data show, sustained effects of treatment persist for many months. Therefore, it is important to randomize the order of the treatments. For this participant, a final one week of stimulation was delivered in order to assess any additional benefit of stimulation since the results of initial month with stimulation + PT were quite marked.

During the stimulation phases of the study, non-invasive, transcutaneous electrical stimulation was delivered to the cervical spinal cord surrounding the injury site (NeuroRecovery Technologies Inc., San Juan Capistrano, CA, USA). The stimulation waveform was biphasic, rectangular, 1 ms pulses at a frequency of 30 Hz, filled with a carrier frequency of 10 kHz (Fig. 3.2) (Gerasimenko, Gorodnichev, Moshonkina, et al., 2015). This permitted stimulation intensities of 80-120 milliamperes (mA) to be delivered to the skin over the cervical spinal cord without discomfort.

Stimulation was delivered via two 2.5 cm round electrodes placed midline at C3-4 and C6-7 spinous processes as cathodes and two 5 x 10 cm2 rectangular plates (Axelgaard Manufacturing Co., Ltd., USA) placed symmetrically over the iliac crests as anodes. A total of 1451 minutes of stimulation was applied over the five weeks (mean duration was 60 ± 20 minutes/session, range 25 - 120 minutes/session).

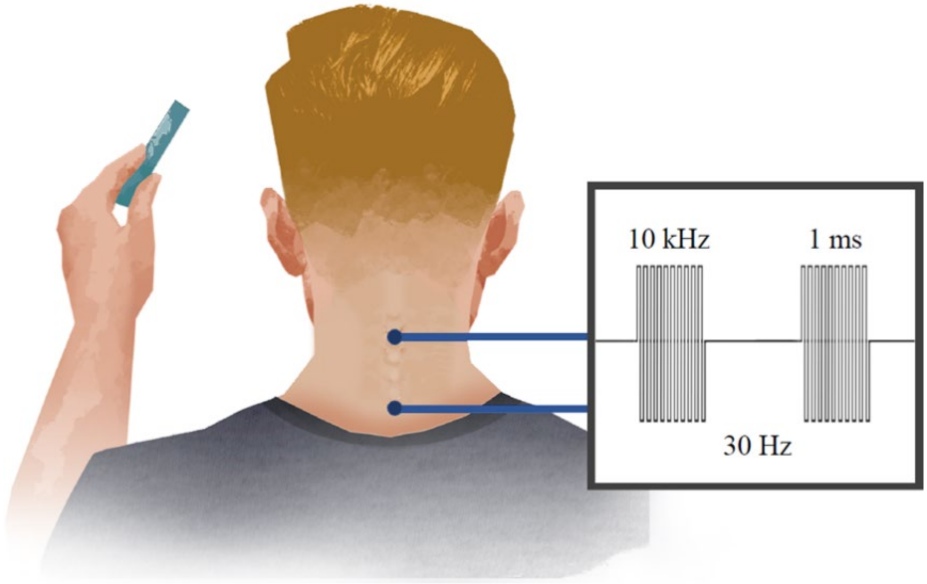


Figure 3.2 Schematic of the intervention showing electrical cervical spinal stimulation applied to the surface of the skin via electrodes placed midline at C3-4 and C6-7 bony landmarks. (Inset) Biphasic, rectangular, 1 ms pulses are delivered at a frequency of 30 Hz. Each pulse is filled with a carrier frequency of 10 kHz to permit stimulation intensities of 80-120mA to pass through the skin and reach the spinal cord without discomfort.

The physical therapy program included standard stretching, active assistive range of motion exercises, and intensive gross and fine motor skill trainings, which resemble most of the daily upper extremity motor tasks (Beekhuizen & Field-Fote, 2005). The total dosage of physical therapy was 58.5 hours over nine intervention weeks, approximately 90 minutes/session. The exact same PT activities were repeated during each phase of the study.

The subject participated in 2-hour sessions, 4-5 days/week, over the 9 weeks of intervention. Blood pressure and heart rate were monitored throughout all sessions. Pinch strength measurements were performed weekly, and reported values represent the average of three consecutive maximal force contractions. GRASSP tests were repeated in the first, second and fourth weeks of stimulation + PT and PT only interventions, and once at the end of the second stimulation + PT phase. During stimulation + PT sessions, tests were repeated both with and without stimulation on successive days in order to avoid fatigue.

Spinal motor evoked potentials from stimulation delivered both at and below the level of injury were recorded at the end of each week of stimulation + PT sessions. The stimulator was set to monophasic, rectangular, 1 ms single pulses at a frequency of 1 Hz (Gad, Roy, et al., 2015; Gerasimenko, Gorodnichev, Moshonkina, et al., 2015; Lavrov et al., 2006). Stimulation intensity was increased in 10 mA intervals from 10 to 120 mA. Motor responses were collected via surface electrodes from eight muscles in each arm (i.e. deltoid, triceps, biceps, brachioradialis, extensor digitorum, flexor digitorum, abductor digiti minimi and thenar muscle groups). A 16 channel Bagnoli electromyography (EMG) system (Delsys, Boston, MA, USA) was used to filter (20-450 Hz) and amplify EMG signals 1000 times. Both the stimulation and EMG signals were digitized at 1 kHz and recorded simultaneously using PowerLab (AD Instruments, Milford, MA, USA). Signals were then rectified, and stimulus triggered averages were subsequently compiled using MATLAB (Matworks Inc., Natick, MA, USA).

During the three-month follow-up period, GRASSP and pinch strengths were retested once every two weeks. ISNCSCI assessment, WHO Quality of Life - BREF, SF-Qualiveen, and SCIM III scores were re-evaluated at the end of each intervention period, and at study completion.

3.4 Results

3.4.1 Baseline outcome measurements

Initial ISNCSCI assessment revealed an AIS category D injury, with a central cord syndrome pattern. Intact light touch sensation was present to C3 and pinprick to C4 dermatomes, bilaterally. The subject had increased muscle tone in all extremities, recorded as 1 - 2 points on the modified Ashworth Scale and experienced infrequent spasms with moderate severity described in Penn Spasm Frequency Scale. On the right side, muscle tone was higher (especially in right biceps and pectoralis muscles) and muscle strength was weaker compared to the left side.

3.4.2 Effect of stimulation on hand and arm function

Cervical transcutaneous electrical spinal cord stimulation + PT resulted in both dramatic and durable improvements in hand and arm function on all motor tasks measured. Upper extremity muscle strength nearly doubled over the course of treatment and stabilized at 75% stronger than baseline for three months without further treatment (Fig. 3.3). Composite scores of ten key muscles of the GRASSP test increased from 41/100 to 78/100 with stimulation treatment and stabilized above 70/100 during the entire follow-up period.

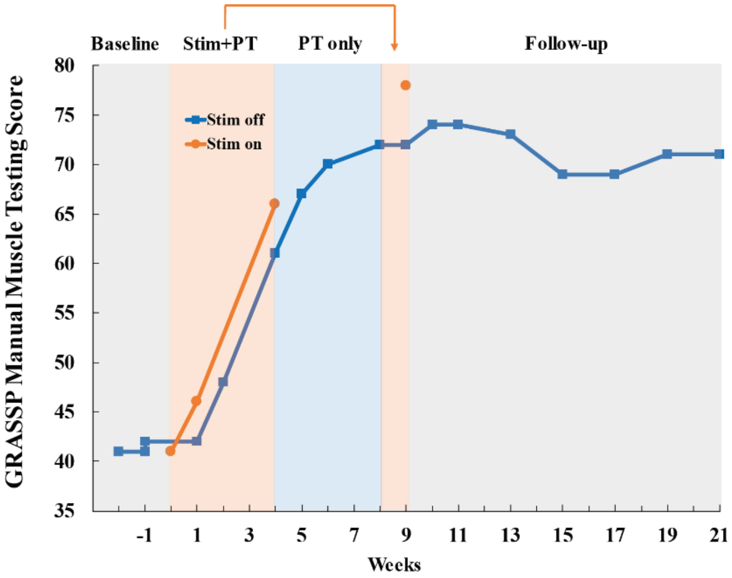


Figure 3.3. Bilateral manual muscle testing scoresDerived from Graded Redefined Assessment of Strength, Sensibility and Prehension (GRASSP) test throughout the study. Motor score is comprised of 10 muscles tested bilaterally (deltoid, triceps, biceps, wrist extensors, finger flexors, finger abductors, extensor digitorum, opponens pollicis, flexor pollicis longus, and first dorsal interossei). Strength is stable during baseline testing, increases 37 points during stimulation combined with physical therapy at week 9, and is maintained during physical therapy only (PT only) and throughout three months of follow-up with no further treatment.

Gains were also observed in all motor function measures of the GRASSP test reflecting restoration of strength, dexterity and prehension. Total GRASSP score improved 56% during the four-week stimulation + PT period (Fig. 3.4). Although stimulation was initially required to achieve such high performance, functional gains were maintained even without stimulation during the entire follow-up period. This 52-point improvement on the total GRASSP score far exceeded the minimal detectable difference of 4-7 points for all sub-scores of the test except fingertip sensation (Fig. 3.5).

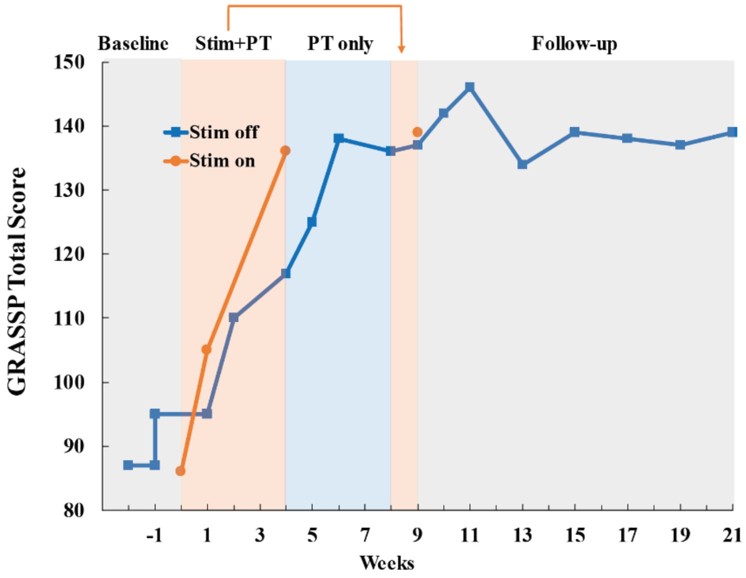


Figure 3.4. **Total GRASSP test scoresTotal GRASSP scores improve markedly during treatment with stimulation and physical therapy. The total score combines all domains of the test including strength, sensation, qualitative and quantitative prehension. Improvements were sustained throughout three months of follow-up with no further treatment. Please see Fig. 3.3 legend for definition of abbreviations, and Fig. 3.5 for results from individual test domains.**

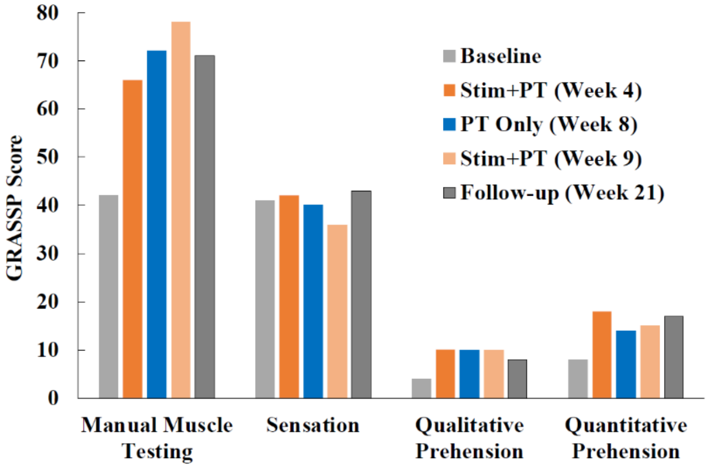


Figure 3.5. GRASSP SubscoresSubscores of the Graded Redefined Assessment of Strength, Sensation and Prehension (GRASSP) testreported at the conclusion of each phase of the study. Improvement (Δ) during stimulation combined with physical therapy (stimulation + PT) exceeded the minimal detectable difference (MDD) for all subscores of the GRASSP test, except fingertip sensation (strength: Δ37 vs. MDD 7; sensation: Δ-2 vs. MDD 4; qualitative prehension: Δ6 vs. MDD 5; and quantitative prehension: Δ11 vs. MDD 6.

Improvements in dexterity and pace of prehension were observed in functional tasks, such as water pouring (cylindrical grasp) and 9-hole peg transfer (tip to tip and three-point pinch). Example videos illustrate the improvements that resulted from treatment with cervical transcutaneous spinal cord stimulation combined with physical therapy (supplementary videos 3.1 & 3.2).

Lateral pinch forces improved rapidly in both hands during the stimulation + PT intervention. Lateral pinch force measured during stimulation increased 2- to 7-fold in the left and right hands, respectively (Fig. 3.6). PT alone did not further improve pinch force, but increase in strengths even without the stimulator active were maintained throughout the three-month follow-up period.

Following only four weeks of stimulation + PT, overall neurological level of injury improved one level caudally from C3 to C4 based on the ISNCSCI exam, and was sustained for the duration of the follow-up with no further treatment. This is unusual based on observations that function either reaches a plateau after one year post injury (Waters, Adkins, Yakura, & Sie, 1993), or increases only gradually from year-one through post injury (Kirshblum, Millis, McKinley, & Tulsky, 2004).

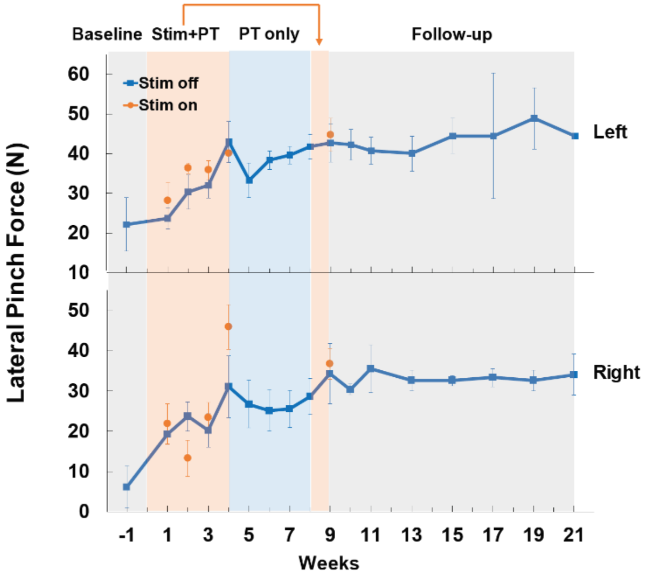
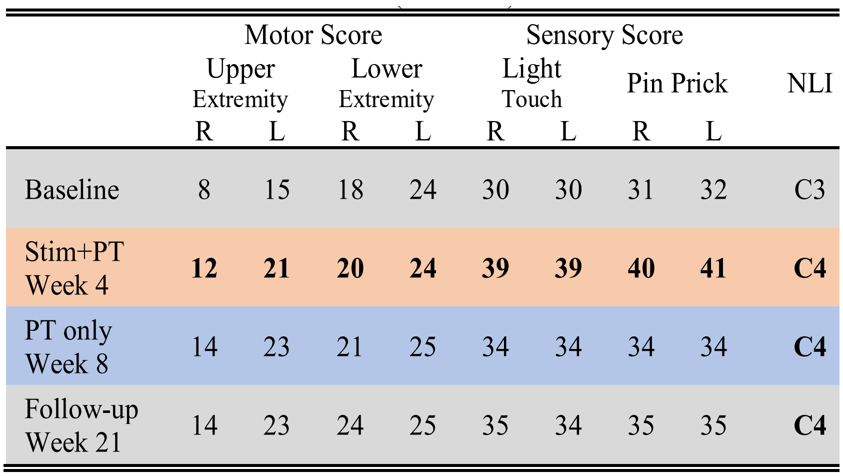


Figure 3.6. Improvement in lateral pinch strengthLateral pinch strength improved in both the right and left hands during stimulation combined with physical therapy. During four weeks of stimulation combined with physical therapy, pinch strength improved 2-to 7-fold in the presence of stimulation for the left and right hand, respectively. Physical therapy alone resulted in no further improvement, but all gains were maintained during three months of follow-up. Each data point is the average of three maximal contractions performed on a given day, and error bars are standard deviation.

Improved neurological level was driven by a combination of motor and sensory recovery. ISNCSCI Upper Extremity Motor Score (UEMS) increased ten points during the four-week stimulation + PT period and an additional four points during PT only sessions (Table 3.1). This new UEMS of 37 out of 50 points remained unchanged throughout follow-up.

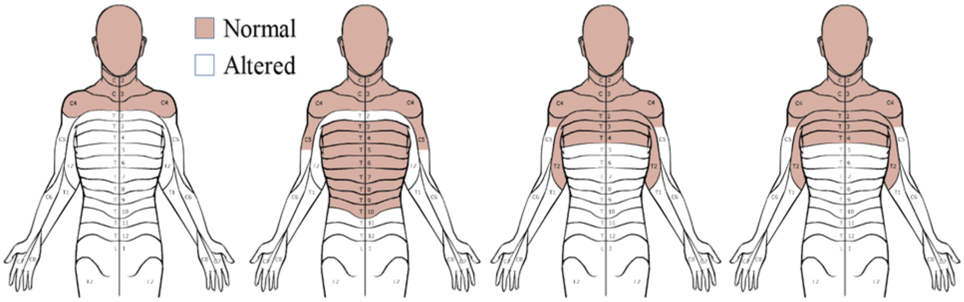
Table 3.1 ISNCSCI assessment



	Motor Score				Sensory Score				
	Upper Extremity		Lower Extremity		Light Touch		Pin Prick		NLI
	R	L	R	L	R	L	R	L	
Baseline	8	15	18	24	30	30	31	32	C3
Stim+PT Week 4	**12**	**21**	**20**	**24**	**39**	**39**	**40**	**41**	**C4**
PT only Week 8	14	23	21	25	34	34	34	34	**C4**
Follow-up Week 21	14	23	24	25	35	34	35	35	**C4**

Stim = Stimulation; PT = Physical therapy;
NLI = Neurologic Level of Injury.

Surprisingly, the subject reported normal pinprick and light touch sensation descending from C4 all the way to the T10 dermatome bilaterally at the end of four-weeks of stimulation + PT (Fig. 3.7). This sensory improvement, however, was only partly sustained at the level of the T4 dermatome without continued stimulation.



Baseline
Stim+PT Week 4
PT only Week 8
Follow-up Week 21

Figure 3.7. Improvement of sensation.Following four weeks of stimulation combined with physical therapy, normal light touch and pin prick sensations expanded from the C4 to the T10 dermatome. After an additional four weeks of physical therapy only, altered sensation returned below T4, but remained constant at this level throughout the three-month follow-up period.

Transcutaneous cervical stimulation + PT also led to improvements in self-care and quality of life. One of the most notable and expeditious functional improvements was observed in self feeding. Within a few minutes of stimulation during the first session, the subject became more smooth and coordinated in both his upper extremity and trunk when performing a self-feeding task compared to the absence of stimulation (supplementary video 3.3). After 4 weeks of stimulation + PT, the participant was very skilled in self-feeding. The subject began partial self-feeding at home on the second week of the intervention for the first time since his injury and continued this activity even after the intervention. Thus, the SCIM III self-care sub score increased one point, which was derived from the self-feeding activity (Table 3.2).

Finally, bladder function improved during treatment. This participant's residual urine volume decreased from 175-200 ml to 100-125 ml at the end of four-weeks of stimulation. Therefore, bladder function related quality of life (SF-Qualiveen) improved 0.5 points out of 4 at the end of stimulation + PT intervention. Most notably, this and all other functional gains were maintained in the absence of stimulation and persisted for over three months of follow-up with no further treatment.

Table 3.2 Disability and quality of life related questionnaires

	Baseline	Stim+PT Week 4	PT only Week 8	Follow-up Week 21
SCIM III*				
Self-care	0	1	1	1
Respiration and sphincter management	21	21	21	21
Mobility	1	1	1	1
Total score	22	23	23	23
WHO-QoL-BREF**				
Physical Health	31	31	44	38
Psychological wellbeing	69	69	69	63
Social relationships	50	56	56	31
Environment	94	88	94	94
SF-Qualiveen***				
Bother with limitations	2.5	1.5	1.5	1.5
Frequency of limitations	4	3.5	3.5	3.5
Fears	0.5	0	0	0
Feeling	1.5	1.5	1	1.5
Overall score	2.125	1.625	1.5	1.625

*Higher scores reflect higher levels of independence

**Scores were transferred to 0-100 point scale. Higher scores denote higher quality of life

***Lower scores reflect higher levels of bladder functions related quality of life

SCIM III = Spinal Cord Independence Measure; WHO-QoL-BREF = World Health Organization Quality of Life questionnaire short version; SF = short form. Other abbreviations as in Table 1.

3.4.3 Effect of stimulation on self-reported functions

Outside of standardized test and measures, the subject and his care giver reported appreciable increases in sensation and locomotion. He reported improvements in proprioception of his lower extremities and a better temperature sensation all over his body especially while showering. On the second week of stimulation, he began walking up and down the stairs with balance assistance using an alternating stepping pattern for this first time since his injury. His step length and balance improved gradually throughout stimulation sessions.

3.4.4 Safety and tolerability of transcutaneous spinal stimulation

No adverse effects were observed throughout the study. Blood pressure and heart rate ranged between 88/58 and 121/85 mmHg and 66-98 beats/minute, respectively. Mild and painless hyperemia was observed under the stimulation electrode site on the neck, which resolved within 5-10 minutes of the completion of stimulation each day. No other skin reaction or irritation occurred. The subject described the stimulation as a continuous and mild tingling sensation on the neck, arms, and the upper trunk without discomfort.

3.5 Discussion

Starting from the very first session of stimulation, almost all motor functions of the hand and arm improved in this participant. Isolated muscle strengths, lateral pinch force, dexterity and pace of prehension tasks improved progressively over the course of treatment using cervical skin surface stimulation combined with physical therapy. The magnitude of these improvements exceeded previous reports of activity- dependent interventions in individuals with subacute or chronic SCI (Beekhuizen & Field-Fote, 2005; Larson & Dension, 2013; Zariffa et al., 2011). The participant also resumed self-feeding for the first time since his injury, resulting in a measurable change in quality of life. Pinprick and light touch sensations returned to the torso, and neurologic level of injury improved from C3 to C4. Most importantly, improved functions persisted throughout the entire three months of follow-up, despite no additional stimulation or physical therapy. This suggests that even a five-week period of transcutaneous spinal cord stimulation and physical therapy can lead to long-term changes in neural circuits and sustained improvements in upper extremity function following spinal cord injury.

Two interrelated mechanism may explain the immediate and sustained improvements in motor and sensory function observed here. The immediate improvements in upper extremity strength and function support the concept that transcutaneous electrical spinal cord stimulation can modulate cervical spinal networks into a physiologic state which enables greater access of supraspinal control to cervical sensory-motor networks. An electrophysiologic study by Hofstoetter et al. recently showed that both epidural and transcutaneous electrical stimulation activates primary afferent fibers within multiple posterior roots (Hofstoetter et al., 2018). The most likely direct mechanism of stimulation occurs via tonic activation of dorsal root afferent fibers which elevates spinal networks excitability. This in turn brings interneurons and motor neurons closer to motor threshold and thus more likely to respond to limited post-injury descending drive (Capogrosso et al., 2013; Gerasimenko et al., 2006; Gerasimenko, Lu, et al., 2015).

It is possible that stimulation of the skin also contributes to elevated neural excitability (Beekhuizen & Field-Fote, 2005; Gomes-Osman & Field-Fote, 2015a; Gomes-Osman, Tibbett, Poe, & Field-Fote, 2017). Hagbarth noted cutaneous stimulation of the cat hindlimb increased afferent fiber activity leading to increased motor neuron excitability (Hagbarth & Naess, 1950).

To what degree transcutaneous stimulation activated the sensory afferent system in the periphery, at the level of the dorsal roots, and/or via the spinal grey matter is currently unknown. The polysynaptic responses in Figure 8 are consistent with a functional enhancement of interneuronal networks, perhaps via a change in reafferent excitability (Hofstoetter et al., 2018). We suggest that the more mechanistically important question is not what is stimulated, but which components of the spinal networks are being modulated by transcutaneous stimulation. Nonetheless, the benefits for hand function appear to be both immediate and sustained following skin surface stimulation in the present study.

Sustained improvements appear to evolve over time and may be explained by gradual neuroplastic change in the spinal networks surrounding the injury. Observed changes in the evoked potentials of networks projecting to the right thenar muscle provide an example of one mechanism that could have facilitated long-term improvements in pinch force. Monophasic stimulation over C3-4 spinous process revealed changes in delayed, polysynaptic responses in the right thenar muscle. This is one of the muscles contributing to the improvements in right hand strength and function. Compared to pretreatment responses, there was a progressive increase in long-latency, likely polysynaptic responses over the month of stimulation combined with physical therapy (Fig. 3.8). Interestingly, this response diminished during physical therapy only, but was rapidly restored by just five additional days of stimulation + PT. This example provides some evidence that transcutaneous electrical spinal cord stimulation leads to both rapid and sustained changes in intraspinal networks.

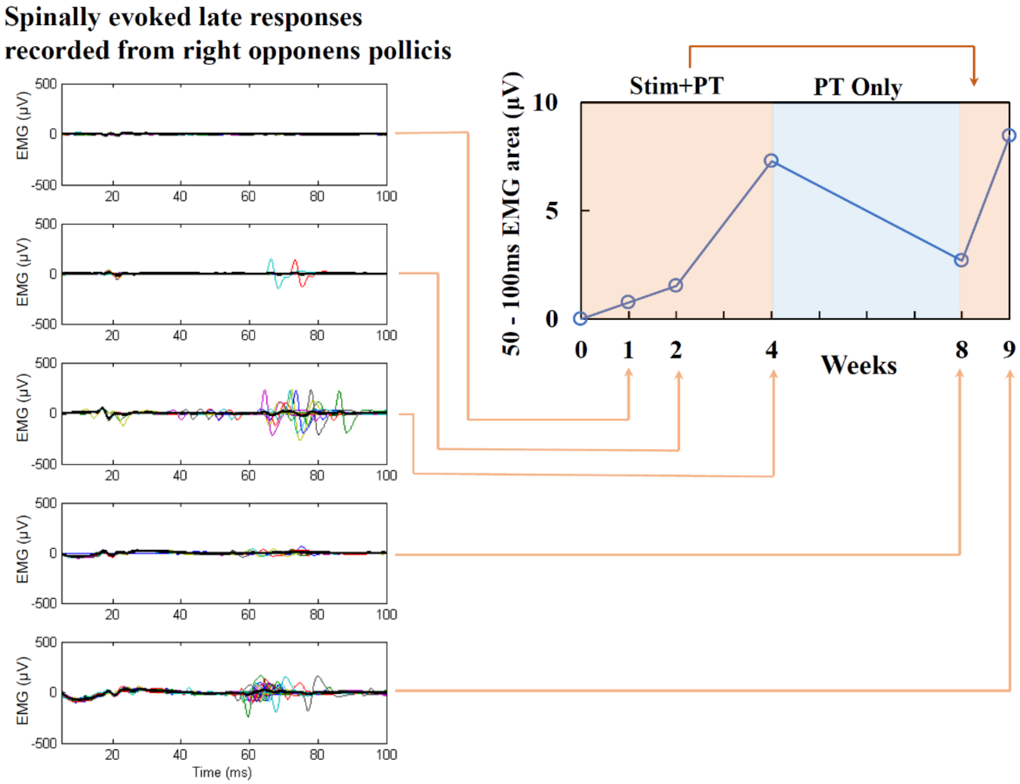


Figure 3.8. Integrated EMG of stimulus-evoked response

Recorded from right opponens pollicis muscle (right panel). Spinal evoked potentials were elicited by monophasic, rectangular, 1 ms single pulses filled with a 10 kHz waveform, delivered at 1 Hz. Stimulation intensity was 90 mA applied over the C3-4 spinous processes. The polysynaptic, late EMG responses (left panels) increased gradually over four weeks of stimulation combined with physical therapy, reduced after physical therapy only, but returned with five days of additional stimulation and therapy treatment.

Furthermore, in this study we show that transcutaneous electrical spinal cord stimulation confers both immediate benefits when the stimulator is active, but also durable improvements in hand and arm function which are sustained for over three-months of follow-up without further treatment. One possible mechanism for this long-lasting functional restoration may be reorganization of cervical spinal networks by intensive task-specific exercise combined with transcutaneous spinal cord stimulation. Specifically, stimulation allows weak but remaining voluntarily-controlled descending drive to produce functional muscle contractions, permitting the participant to engage in intensive therapy which subsequently strengthens these neuro-muscular networks (Gomes-Osman & Field-Fote, 2015b). Thus, at the conclusion of treatment, stimulation is no longer required to achieve robust volitional control of hand movements after spinal cord injury.

Similar to long-term improvements in volitional motor control, return of normal sensation below the injury in the present study may be explained by enhanced excitability of sensory networks. This enhanced activity may facilitate initially weak ascending sensory connections passing the injury site to restore partial sensory function even beyond the period of stimulation.

The findings of the current study extend those of Lu et al., who studied the effect of cervical epidural electrical stimulation in two subjects with chronic motor complete (AIS B) tetraplegia (Lu D. C. et al., 2016). The indication for implantation of epidural stimulator was refractory chronic pain for both subjects. The authors demonstrated improved maximum grip force and volitional motor control both during and shortly after epidural stimulation. Despite the dissimilarities of injury level, severity and outcome measures used, the results of our study are largely comparable with cervical epidural stimulation. Excitingly, transcutaneous spinal stimulation appears to result in similar improvements as epidural stimulation, without the need for implanted electrodes.

Taken together, findings of the current study (1) show that the effect of stimulation is both immediate and long-lasting, (2) provide evidence that electrical neuromodulation of the cervical spinal cord combined with activity based exercise therapy can promote substantial functional recovery of upper extremities in chronic SCI, and (3) demonstrate the therapeutic potential of non-invasive electrical spinal cord stimulation for people with cervical SCI. Future work is needed to explore the exciting potential of transcutaneous spinal stimulation and optimize its ability to restore function following a range of neurological injuries.

3.6 Legends to the supplementary videos

Supplementary Video 3.1. Illustration of improvements in the “Pour the water into the cup” task that evaluates cylindrical grasp function. This is one of the prehension tasks of the standardized GRASSP test. During baseline evaluations the participant was unable to grasp the bottle and lift it off the table, hence the lid was left secured to the water bottle. During stimulation combined with physical therapy sessions, dexterity for grasping and strength for raising/manipulating the bottle developed progressively such that the participant could reliably hold and position the bottle over the cup by the fourth week. During the final stimulation period in the ninth week, we were confident to open the bottle and he succeeded in the complete water pouring activity. For this task, performance was better when the stimulator was on compared to trials with the stimulator off (later not shown).

Supplementary Video 3.2. Performance in the standardized 9-hole peg test indicating improved tip-to-tip or three-point pinch function of the hand. During baseline evaluations, the participant could neither grasp the pegs nor transfer and place them in the holes on the opposite side of the board. Similar to other functional tasks, both the pace and number of transferred pegs improved throughout the stimulation combined with physical therapy intervention. By the 4th week of stimulation treatment, the participant could complete the test even without the stimulator active, although performance was nearly twice as fast during stimulation.

Supplementary Video 3.3. Examples of a simulated self-feeding activity. Immediately before the first stimulation treatment session, the participant was uneasy and clumsy in performing the self-feeding activity. He used a compensatory posture of the trunk to reach the spoon. Following just several minutes of stimulation on the first day of treatment, however, his left arm and hand movements became evidently smoother and more coordinated, with a more stable posture of the trunk. Progressive improvement was noted throughout the four weeks of stimulation treatment sessions. The participant began self-feeding at home during the second week of stimulation and for the first time since his injury.

Acknowledgment

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Chapter 4 Non-invasive spinal cord stimulation restores hand function after paralysis

This chapter is submitted for publication.

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4.1 Abstract

Paralysis of the hands severely restricts independence and quality of life after spinal cord injury. Regaining control of hand and arm movements is the highest treatment priority for people with paralysis, 6-fold higher than restoring walking ability (Anderson, 2004). Nevertheless, current approaches to improve upper limb function are largely ineffective. Spinal cord stimulation is an emerging neuromodulation strategy to restore motor function (Edgerton & Roy, 2012; James et al., 2018). Recent studies using surgically implanted electrodes demonstrate impressive improvements in voluntary control of standing and stepping (Angeli et al., 2018; Angeli et al., 2014; Grahn et al., 2017; Harkema et al., 2011; Wagner et al., 2018). Here we show that non-invasive electrical stimulation of the spinal cord leads to rapid and sustained recovery of hand function, even after complete paralysis. Notably, the magnitude of these improvements matched

or exceeded previously reported results from surgically implanted stimulation (Lu D. C. et al., 2016). Additionally, muscle spasticity was reduced and autonomic functions including heart rate, thermoregulation, and bladder function all improved. Perhaps most notable is that all six participants maintained their gains for at least three to six months beyond stimulation, indicating functional recovery mediated by long-term neuroplasticity. Several participants resumed their hobbies that require fine motor control, such as playing the guitar and oil painting, for the first time in up to 12 years since their injuries. Our findings demonstrate that non-invasive electrical stimulation of the spinal networks restores movement and function of the hands for people with both complete paralysis and long-term spinal cord injury.

4.2 Introduction

Damage to the spinal cord interrupts the communication between the brain and the body that can results in permanent paralysis. At present, there is no cure for spinal cord injury (Chen & Levi, 2017). There is recent evidence, however, that the spinal cord below an injury can be activated with electrical stimulation in order to restore conscious control of movement (Harkema et al., 2011; Lu D. C. et al., 2016; Wagner et al., 2018).

Ongoing electrical stimulation of the spinal cord surface via implanted epidural electrodes is typically required to enable movement of paralyzed limbs (Angeli et al., 2018; Gill et al., 2018; Harkema et al., 2011; Wagner et al., 2018). The ultimate goal of rehabilitation, however, is to promote recovery of neuronal pathways connecting the brain and spinal cord such that stimulation is no longer required (Behrman, Ardolino, & Harkema, 2017). Intensive exercise training attempts to promote such adaptation and neuroplasticity in the injured spinal cord to produce permanent recovery after injury (Behrman et al., 2017; L. R. Hoffman & Field-Fote, 2010). By combining these approaches, electrical stimulation of the spinal cord may initially enable movement[2] such that individuals can participate in intensive training programs and achieve long-term recovery of function.

The use of electrical stimulation to enable rehabilitation has led to impressive restoration of leg movement and stepping using implanted epidural stimulation in individuals with both motor complete and incomplete spinal cord injury (Angeli et al., 2018; Gill et al., 2018; Wagner et al., 2018). Despite the paramount importance after spinal cord injury, only a few studies focused on the effect of epidural spinal cord stimulation to restore hand and arm function (M. M. Dimitrijevic et al., 1986; Lu D. C. et al., 2016; Waltz et al., 1987), and none were combined with intensive rehabilitation training to facilitate activity-dependent plasticity.

While impressive functional gains have been reported with implanted epidural stimulation electrodes, a new method of non-invasive spinal stimulation has recently emerged. By adopting a 10 kHz overlapping-frequency (Ward & Robertson, 1998), transcutaneous spinal cord stimulation allows application of high stimulation intensities through the skin surface that can reach the spinal cord without causing discomfort (Gerasimenko, Gorodnichev, Moshonkina, et al., 2015; Inanici et al., 2018). Even without intensive exercise training, non-invasive cervical spinal cord stimulation demonstrated promising potential to improve hand function in people with tetraplegia (Freyvert et al., 2018; Gad, Lee, et al., 2018).

4.3 Methods

4.3.1 Study Design

We conducted a prospective, open-label, two-arm study. We began by repeating baseline measurements once per week for four weeks to evaluate each participant's functional variability over time and to control for learning effects of the outcome measures. The intervention began with four weeks of intensive functional task training following a specified protocol, followed by four weeks of transcutaneous electrical cervical spinal cord stimulation paired with the same training (Fig. 4.1). The order of the subsequent treatment arms was determined for each participant. We continued delivering stimulation to participants with motor complete injuries (AIS B), and interleaved blocks of training alone for those with incomplete injuries (AIS C-D). We interleaved blocks of treatment for participants with incomplete injuries to definitively test whether stimulation contributed to the observed improvements as opposed to improvements simply accumulating over time.

The study was designed to follow participants for three months after the last treatment to document the persistence of functional gains without further intervention. All participants returned for monthly follow-up visits for at least three months, with one exception. Participant 1 was unavailable during the third month of follow-up, and instead returned 6 months after treatment for his final visit. Participant 3 also returned for an additional visit six months after treatment. The remaining participants were not eligible to return for this extra follow-up visit due to enrolling in other studies or receiving Botulinum Toxin injections at the conclusion of our study. All procedures were approved by the University of Washington Institutional Review Board (STUDY00002985). The study was registered with ClinicalTrials.gov (NCT03184792).

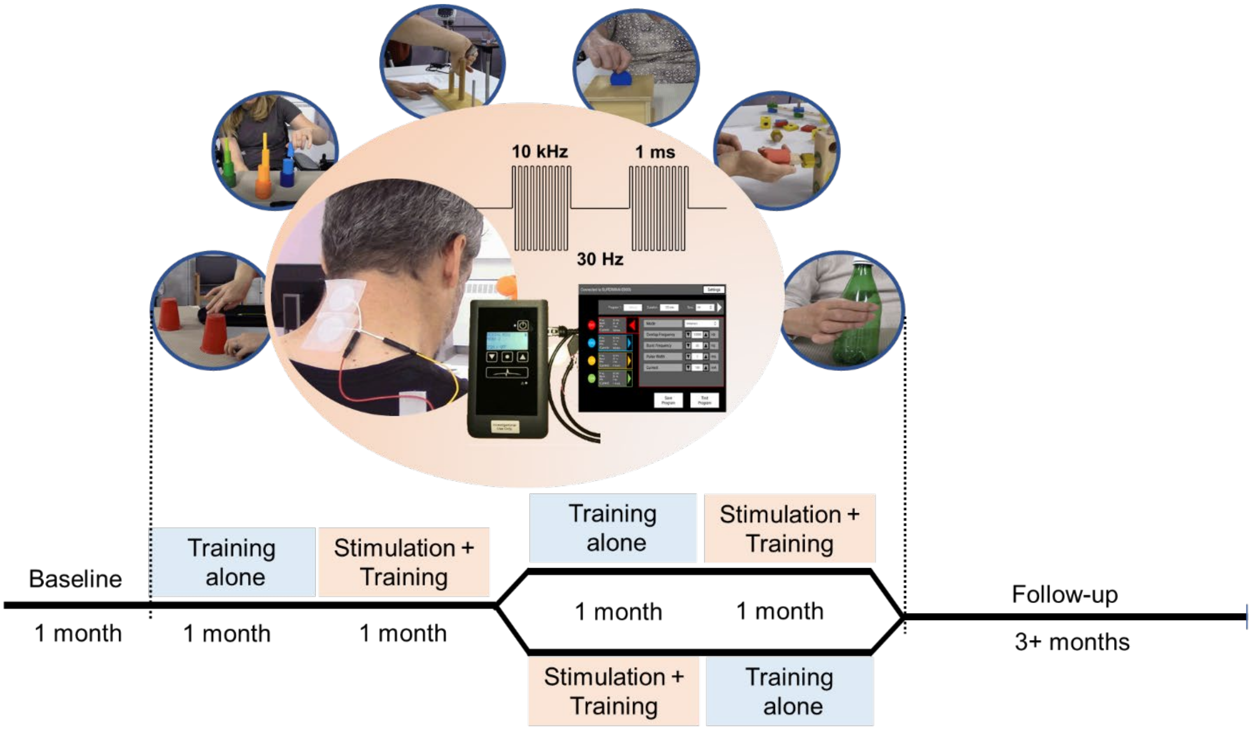

Figure 4.1 Study design and timetable. A prospective, open-label, cross-over study. Outcome measurements were repeated weekly during baseline, every 2 weeks throughout the treatment period, and once a month during follow-up. We delivered training alone during the first month of treatment, and stimulation paired with training during the second month for all participants. For the last two months of treatment, the order was determined by each participant's injury severity. We continued delivering stimulation to participants with motor complete injuries (AIS B), and interleaved a second month of training alone for those with incomplete injuries (AIS C-D). Training: Intensive functional task training; Stimulation: 1 ms bursts of 10 kHz transcutaneous cervical spinal cord stimulation delivered at 30 Hz.

4.3.2 Participants

Six volunteers with chronic cervical spinal cord injury participated in the study. Mean age of the participants was 42 years (SD ± 14, range 28 - 62) and mean time since their injury was 4.6 years (SD ± 3.8, range 1.5 - 12). Demographics and clinical characteristics of the participants are listed in Table 4.1. All participants gave written informed consent for all study procedures, including usage of video recordings/images. Participants three and four further consented to share their identifiable images in scientific publications. Inclusion and exclusion criteria are itemized in Table 4.2.

Table 4.1 Demographic and clinical characteristics of participants

Participant	Age	Gender	Time since injury (years)	NLI	AIS category	INSCSCI UEMS
1	28	M	1.5	C5	B	24
2	33	M	4	C5	B	19
3	44	M	12	C5	C	38
4	32	F	5	C5	D*	43
5	62	F	2.5	C5	C	36
6	57	M	2.5	C3	D*	28

NLI: Neurologic Level of Injury
AIS: American Spinal Cord Injury Impairment Scale
ISNCSCI: International Standards for Classification of Spinal Cord Injury
UEMS: Upper Extremity Motor Score
M: male; F: female
* Central cord syndrome: paralysis in the arms and hands is more severe than the lower limbs

Table 4.2 Inclusion and exclusion criteria

Inclusion criteria:

- age between 21 and 70 years
- a traumatic spinal cord injury in the neck (C7 or higher level)
- at least one-year post-injury
- stable medical condition without cardiopulmonary disease or frequent autonomic dysreflexia that would contraindicate participation in upper extremity rehabilitation or testing activities
- difficulty independently performing hand and arm function in routine activities of daily living
- capability of performing simple cued motor tasks

Exclusion criteria:

- etiology of spinal cord injury other than trauma
- dependency on ventilation support
- concomitant neurologic disease, such as traumatic brain injury, multiple sclerosis, stroke, and peripheral neuropathy
- significant medical disease; including uncontrolled systemic hypertension with values above 170/100 mmHg; cardiac or pulmonary disease; chronic contagious disease, uncorrected coagulation abnormalities or need for therapeutic anticoagulation
- unhealed fracture, contracture, pressure sore, urinary tract infection or other illnesses that might interfere with upper extremity rehabilitation or testing activities
- botulinum toxin injection in upper extremity muscles in the prior 6 months
- tendon or nerve transfer surgery in the upper extremity
- any implanted stimulator in the body, such as vagus nerve stimulator, cardiac pacemaker, cochlear implant, etc.
- depression, anxiety or cognitive impairment based on Patient Health Questionnaire-9 (Kroenke, Spitzer, & Williams, 2001) (score >9/27), General Anxiety Disorder-7 item Questionnaire (Spitzer, Kroenke, Williams, & Lowe, 2006) (score >9/21), and Short Portable Mental Status Questionnaire (Roccaforte, Burke, Bayer, & Wengel, 1994) (score >2/10)
- pregnancy
- active cancer
- alcohol and/or drug abuse
- inability to read and/or comprehend the consent form

4.3.3 Intensive functional task training

Upper limb motor training occurred three times per week and two hours per session. We used activity-based rehabilitation comprised of intensive, progressive, functional task training following a protocol. The protocol consisted of repetitive unimanual and bimanual activities of gross upper limb movement, isolated finger movements, bimanual task performance, simple and complex pinch, and grip performance (Beekhuizen & Field-Fote, 2005; Hoffman & Field-Fote, 2013; Hoffman & Field-Fote, 2010). For each category, 8-10 activities with various difficulty levels were designated, and the participant performed 1-2 activities within each category in each training session. Activities were chosen according to the participant's ability and were changed or modified as function progressed over time. For instance, the size of the coins was reduced for a pinch grip task, or resistance level was increased for TheraPutty exercises. Typical movement patterns (Vergara, Sancho-Bru, Gracia-Ibanez, & Perez-Gonzalez, 2014) were encouraged by guidance and giving feedback. When the subject had little to no voluntary movement, active assistance was provided. We encouraged 3-5 minutes rest periods between activities and when needed.

4.3.4 Transcutaneous electrical spinal cord stimulation

We delivered transcutaneous electrical spinal cord stimulation to the cervical spinal cord utilizing the experimental device developed by NeuroRecovery Technologies Inc. (San Juan Capistrano, CA, USA). The device was approved for use in research by the University of Washington Scientific Instruments Division. The stimulator delivers programmable electrical current waveforms that are comprised of two modulated frequencies: (1) base frequency and (2) overlapping frequency, on up to four independent channels (Fig. 4.1 inset). This current waveform is adapted from kilohertz-frequency muscle stimulation, and permits high amplitude stimulation without discomfort (Ward, 2009; Ward & Shkuratova, 2002). Thus, stimulation over the skin can reach the spinal cord to activate spinal networks (Hofstoetter et al., 2018). The rationale for the high overlapping frequency is that unmyelinated C-fibers in the skin can be selectively blocked by using high-frequency waveforms (Joseph & Butera, 2011; Ward & Robertson, 1998), and stimulation may penetrate more deeply due to lowering of the tissue impedance (Medina & Grill, 2014).

We used an electrical current waveform for transcutaneous spinal cord stimulation that was either biphasic or monophasic, 1 millisecond pulse width, 30 Hz base frequency, with a 10 kHz overlapping frequency (Figure 4.1 inset). Stimulation intensity was adjusted between 0 and 120 milliamperes (mA) using a wireless tablet as a programmer. In this study, we used two 2.5 cm round self-adhesive hydrogel surface electrodes as cathodes and two 5 x 10 cm rectangular self-adhesive hydrogel plates as anodes (Axelgaard Manufacturing Co., Ltd., USA). Cathode electrodes were placed midline on the skin of the neck, one above and one below the injury level with the guidance of the occipital inion and spinous processes as landmarks. Anode electrodes were placed symmetrically over the iliac crests of pelvis.

We determined the optimal stimulation parameters for each participant based on the motor responses that were tested in the first session of stimulation. Subthreshold stimulation intensity was used for therapeutic stimulation. Monophasic and biphasic stimulation waveforms activate neural circuits differently (Wang, Millard, Zheng, & Stanley, 2012), and both waveforms were tested for their ability to enable functional movements. We increased the stimulation intensity in increments of 5 mA until muscle tone began to reach a level that interfered with coordination. We typically observed enhanced volitional control over weak or paralyzed muscles between 40-90 mA stimulation intensities. This was always below levels that caused any direct muscle activation.

Stimulation was delivered for up to 120 minutes during each session of stimulation paired with intensive upper limb training. For safety precautions, we closely monitored heart rate and blood pressure throughout each session. Stimulation was well tolerated by all participants. We did not observe any significant adverse events related to transcutaneous spinal cord stimulation or intensive functional task training. Stimulation parameters were re-adjusted as needed throughout the intervention phase of the study. For example, fine motor skills required less stimulation current than strengthening exercises for some participants.

4.3.5 Outcome measures

The primary outcome measure was the Graded Redefined Assessment of Strength, Sensibility, and Prehension (GRASSP) version 1.0 (Kalsi-Ryan, 2014; Kalsi-Ryan et al., 2012) (Neural Outcomes Consulting Inc. Toronto, ON, Canada). Secondary outcomes included the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) exam (Kirshblum et al., 2011), pinch force measurements, and clinical assessment of spasticity.

Pinch force was measured for both the right and left hands (Echo wireless and IRIS software; JTech Medical Industries, Inc. Midvale, UT, USA). To avoid tenodesis movement, tests were performed in a standardized way with participants seated upright against the back of their wheelchair, shoulder adducted and neutrally rotated, elbow flexed 90 degrees, and forearm in the neutral position as much as possible given muscle tone (Angst et al., 2010). Verbal encouragement was provided to the subjects to exert maximum force. Visual feedback of force was not provided. The average of three maximal force measurements per test session is reported (Angst et al., 2010).

Spasticity was graded by the Modified Ashworth Scale (MAS) (Bohannon & Smith, 1987). A total MAS score was calculated by adding five upper extremity scores from each arm and hand (shoulder abduction; elbow extension and supination; and wrist extension; and finger extension) (range 0 – 40, 1+ grade was calculated as 1.5 points). Additionally, the Spinal Cord Independence Measure III (SCIM III) (Bluvshtein et al., 2011) self-care subdomain, and the WHO Quality of Life – BREF (Skevington et al., 2004) questionnaire were administered to capture improvements in independence and quality of life.

GRASSP test and pinch force measurements were repeated once every week at baseline, every two weeks throughout the interventions and every month during the first three months of follow-up. Measurements were performed with and without stimulation in random order during all stimulation combined with training intervention periods. These measurements were done on consecutive days to avoid fatigue. All other measurements were repeated once at baseline, at the end of each treatment block and during monthly follow-up visits.

4.3.6 Data analyses

For comparison of the functional changes over the study periods, we used one-way repeated measures ANOVA, with post hoc pairwise analysis as per Tukey LSD test (IBM SPSS version 26). A Shapiro-Wilk Test showed that repeated measurements followed a normal distribution. Mauchly's test was used to analyze the assumption of sphericity, and degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity when the assumption was violated.

We directly compared the benefits of training alone and stimulation combined with training by calculating the cumulative changes in each outcome measures across each intervention arm. These values were normalized to baseline to control for individual variation in function when beginning the study, and compared between training and stimulation + training interventions using a paired samples t-test.

For all tests, $p < 0.05$ was considered significant. Each individual's data points were included in all analyses. Group data displays individual values as dot plots and mean ± standard error of the mean (SEM) as bar plots. Given the early stage of research and lack of prior data on transcutaneous spinal cord stimulation for restoring upper limb function, power analysis and sample size were not computed. The datasets generated during the current study are available from the corresponding author on reasonable request.

4.4 Results

Here we show for the first time the ability of transcutaneous spinal cord stimulation paired with intensive functional task training to restore prolonged upper limb function in six people with both motor complete and incomplete cervical spinal cord injury. We directly compared improvements during the application of training alone to stimulation paired with training, as well as long-term benefits that persist beyond stimulation.

All participants were injured more than one year prior to joining the study (Table 4.1). They first received one month of intensive upper extremity exercise training, followed by transcutaneous stimulation paired with the same training (Fig. 4.1). An additional month of training alone and stimulation combined with training was delivered in an order based on their injury severity.

People with complete paralysis due to spinal cord injury typically do not recover significant function beyond the first year after injury. Our first participant with such motor complete paralysis had no active movement of his fingers or thumbs when he joined the study. His hands remained paralyzed despite four weeks of intensive training (Fig. 4.2a). It was only during four subsequent weeks of transcutaneous stimulation paired with training that he began to move his fingers and thumbs for the first time since his injury. This restored movement allowed him to produce pinch force between his fingers and thumb in both hands (Fig. 4.2a). Four additional weeks of stimulation paired with training nearly doubled the force he could produce in both hands, whereas four additional weeks of training alone had no effect. Most notably, his gains in movement and pinch force were maintained for at least six months of follow-up without any further treatment (Fig. 4.2a).

Similar results were observed for our second participant with a motor complete injury who had no functional finger and thumb movement at baseline (Fig. 4.2b). These results indicate that pairing of transcutaneous stimulation and training has evident and lasting benefits for people with motor complete cervical spinal cord injury.

Our remaining four participants joined the study with some ability to move their fingers and thumbs. Some of these participants responded almost instantly to stimulation. For example, after 12 years of severe weakness following spinal cord injury, our third participant regained the ability to manipulate small objects on the first day of stimulation (Supplementary video 4.1). By the second day of stimulation, this participant could grasp much smaller objects (Supplementary video 4.2).

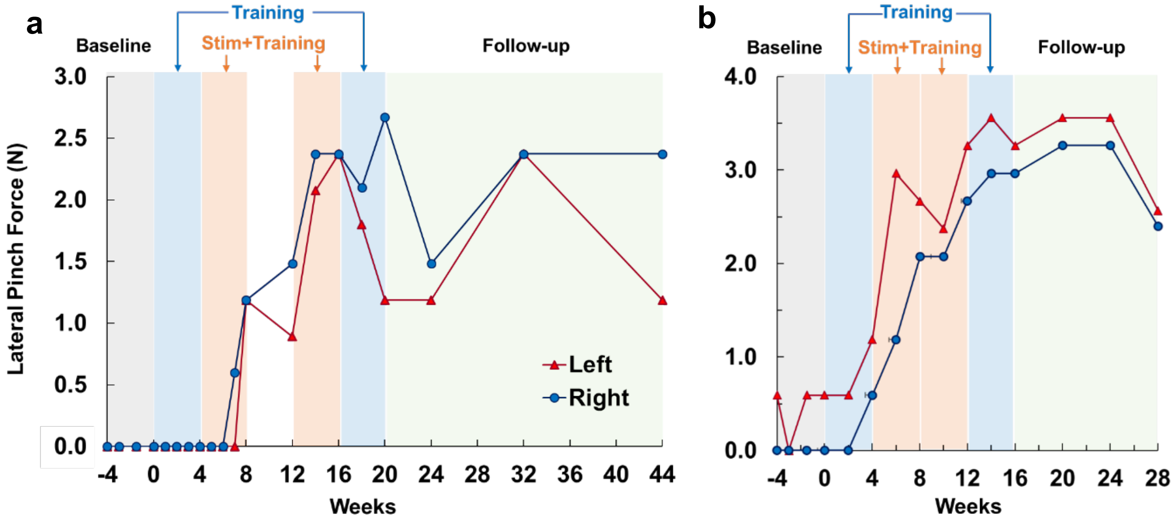

Figure 4.2. Pinch force improvements Transcutaneous spinal cord stimulation paired with intensive training enabled two paralyzed participants to regain movement and pinch force. a. Participant 1 sustained a C5 level motor complete injury (AIS B) 1.5 years prior to beginning the study. He had no active movement distal to both wrists at baseline and throughout the first four weeks of training alone. Only with stimulation (stim) paired with training did this participant regain volitional movement of his fingers and thumbs that enabled him to produce measurable pinch force. Pinch force was sustained over a 4-week vacation leave between the first and second periods of stimulation. An additional four weeks of stimulation treatment nearly doubled pinch force again in both hands. Most notably, these gains in movement and pinch force were maintained for six months of follow-up without further treatment. Although there was a slight downward trend toward the end of follow-up, his function was not below that measured during the final phase of training alone. b. Participant 2 began the study 4 years after a C5 level AIS B spinal cord injury. Pinch force in both hands improved rapidly during stimulation paired with training, and were largely sustained for three months of follow-up without further treatment. For both participants, transcutaneous stimulation was monophasic, 1 ms pulse width, 30 Hz frequency with 10kHz overlapping frequency (Fig 1 inset), and 40 – 90 mA pulse amplitude. No stimulation or training were provided during baseline and follow-up periods indicated by gray and green shaded areas, respectively.

Active stimulation was initially required for improved hand function in this third participant, as measured by the Graded Redefined Assessment of Strength Sensation and Prehension (GRASSP) test (Fig. 4.3). Within one month of stimulation and training, however, he could achieve a high level of function even without stimulation. An additional month of stimulation further enhanced the outcomes that were retained at least three months after the end of all treatment. (Fig. 4.3).

Similar benefits of improved strength and grasping ability were observed in all participants. Performance was significantly higher at the end of stimulation compared to training alone for pinch force, arm and hand strength, and dexterity (Fig. 4.4 a-c, $p < 0.025$, paired-samples t-test, Table 4.3). For example, pinch force improved between 2.4- and 4.8-fold during stimulation combined with training compared to baseline levels.

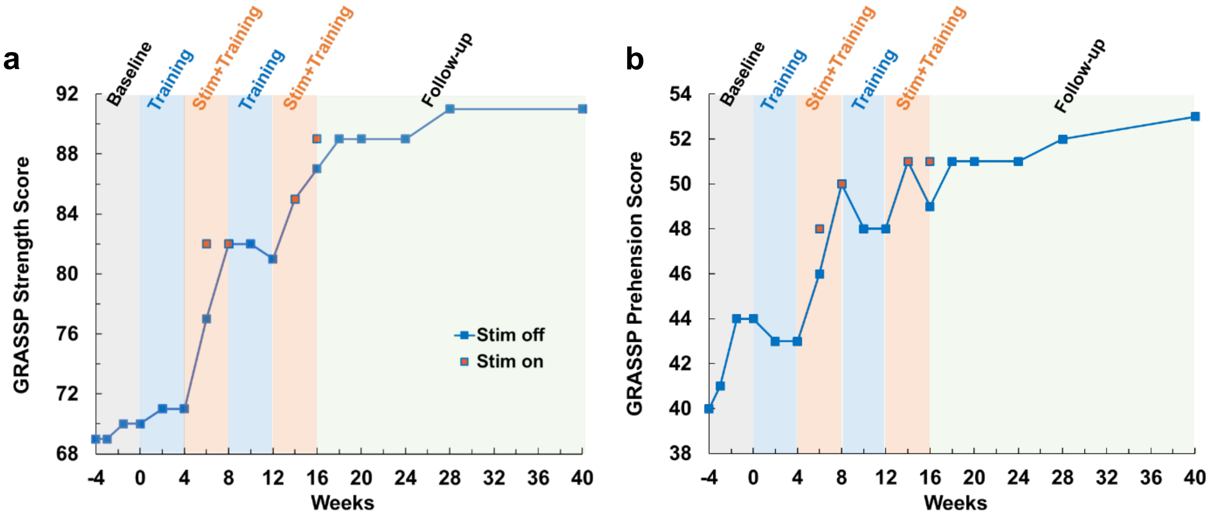

Figure 4.3. Typical progression in strength and quantitative prehensionMeasured by the Graded Redefined Assessment of Strength Sensation and Prehension (GRASSP) test. Participant 3 began the study 12 years after an injury classified as C5 AIS C. a. Bilateral strength score represents manual muscle testing of 10 muscles in each arm. Strength improved by only 2 points during each phase of baseline testing and training alone. The participant became 11 points stronger during the first four weeks of stimulation paired with training. During the first 2 weeks of stimulation, maximum strength gains required the stimulator to be active (orange symbols). After an additional two weeks of stimulation, however, the same strength was measured without stimulation (blue & orange symbols overlap). b. **Prehension score represents unimanual performance of 6 tasks in GRASSP test. There was no increase in score during training alone. In contrast, quantitative prehension improved by 7 points during the first month of stimulation and training and 3 points further during the second month of stimulation and training. All improvements were sustained throughout 6-months follow-up. Transcutaneous stimulation parameters for this participant were both monophasic and biphasic, 1 ms pulse width, 30 Hz frequency with a 10kHz overlapping frequency, 40 – 55 mA pulse amplitude.**

Table 4.3 Results of paired samples T-test for cumulative improvements

	Training alone	Stimulation + Training							
	Mean (SEM)	Mean (SEM)	n	95% CI for Mean Difference	r	t	df	p-value	Cohen's *d*
GRASSP Strength	3.8 (1.2)	14.2 (3.1)	6	3.7, 17.0	0.61	4.00	5	0.010	1.63
GRASSP Prehension	0.7 (1.1)	10.2 (1.2)	6	6.6, 12.4	0.54	8.50	5	0.000	3.75
Pinch Force	3.0 (1.5)	11.5 (3.9)	6	1.7, 15. 3	0.90	3.22	5	0.024	1.34

All but one participant exceeded the minimal detectible difference of GRASSP strength (7 points) and prehension (6 points) subscores during stimulation paired with training.
SEM: standard error of the mean; n: sample size; r: correlation coefficient; t: test statistics, df: degrees of freedom, Cohen's *d*: effect size

Stimulation allowed the participants to engage more fully in the training exercises by permitting activation of previously weak or paralyzed muscles. This led to functional improvements that persisted for three to six months beyond the stimulation in all participants (Fig. 4.4 d-f, Table 4.4). One-way repeated measures ANOVA confirmed significant differences over the study in pinch force ($F(1.1,5.3) = 8.8$, $p = 0.029$), GRASSP test measures for strength ($F(2,10) = 18.0$, $p < 0.001$) and quantitative prehension ($F(2,10) = 49.3$, $p < 0.001$). Post-hoc comparisons showed that all measures were significantly greater at the end of stimulation than training alone, whereas the differences between baseline and training alone were non-significant except GRASSP strength. Finally, all functional improvements were sustained for three to six months of follow up; all measures were significantly greater ($p \leq 0.045$) at the final follow-up visit compared to baseline (Fig. 4.4 d-f, Table 4.4).

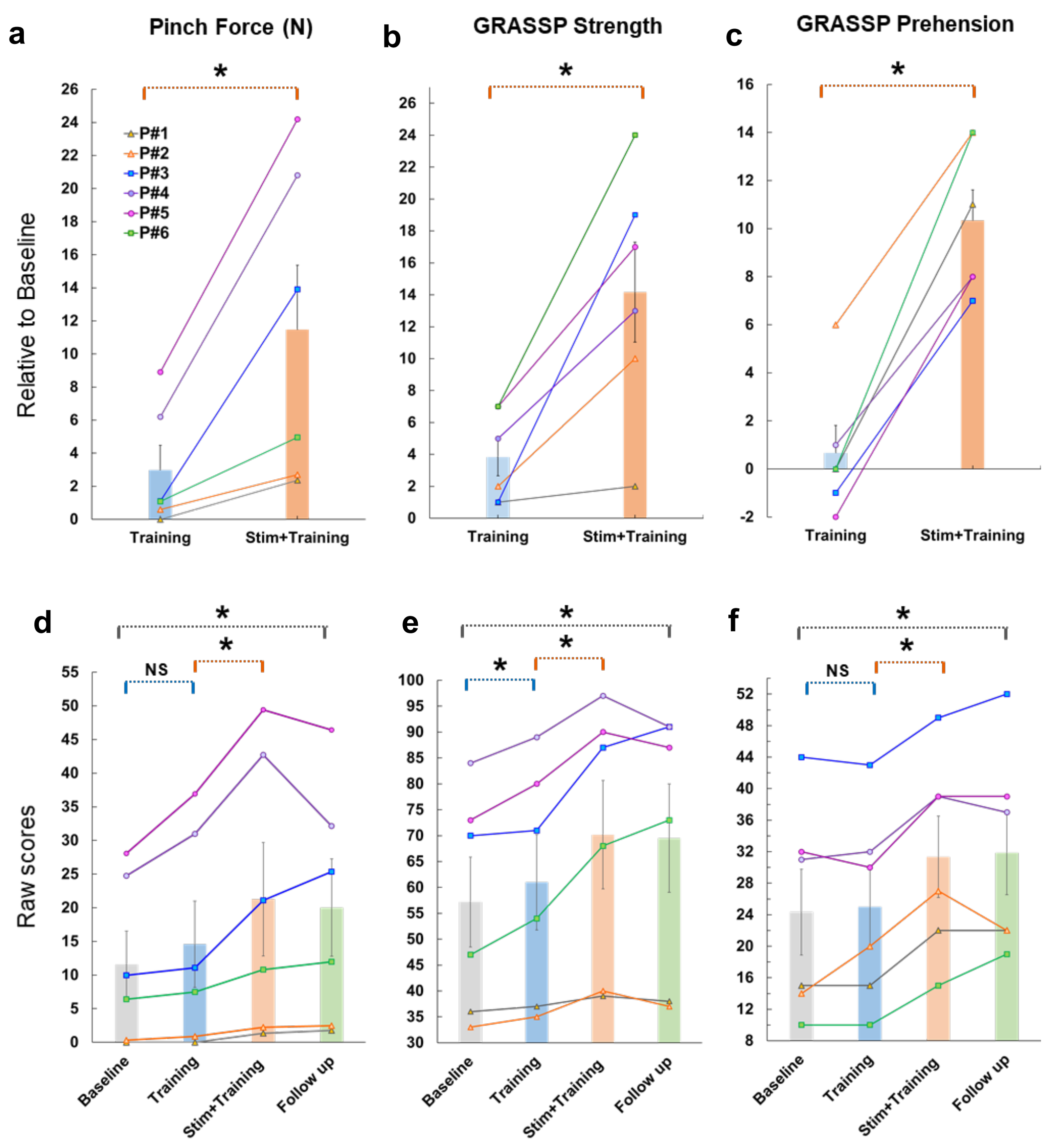

Figure 4.4. Cumulative scoresAll six participants improved hand function during transcutaneous stimulation paired with training, and maintained those gains throughout three to six months of follow-up. (a-c). Stimulation combined with training led to greater improvements than training alone in bilateral pinch force ($t(5) = 3.2$, $p = 0.024$), GRASSP strength ($t(5) = 4.0$, $p = 0.010$), and prehension ($t(5) = 8.5$, $p < 0.001$; paired sample T-test) (d-f). Improvements that occurred during stimulation paired with training were maintained for at least 3 to 6 months of follow-up; all measures were significantly greater at final follow-up visit than baseline ($p \leq 0.045$; one-way repeated measures ANOVA and Tukey LSD pos-hoc). All outcome measures were significantly greater at the end of stimulation than training alone ($p \leq 0.022$), and only the GRASSP strength improved due to training alone (Table 4.4).

***: $p < 0.05$; NS: $p > 0.05$**

Table 4.4 Results of one-way repeated measures ANOVA

	Mean (SEM)						
	1	2	3				
	Baseline	Training alone	Stimulation +Training	$F(2,10)$	p	η_p^2	Tukey LSD
GRASSP Strength	57.2 (8.7)	61.0 (9.2)	71.3 (10.4)	18.0	0.000	0.783	1 vs.2: p = 0.022 1 vs.3: p = 0.006 2 vs.3: p = 0.010
GRASSP Prehension	24.3 (5.4)	25.0 (5.0)	34.7 (4.3)	49.3	0.000	0.908	1 vs.2: p = 0.586 1 vs.3: p = 0.000 2 vs.3: p = 0.000
				$F(1.1,5.3)$			
Pinch Force*	11.6 (5.0)	14.6 (6.4)	23.1 (8.8)	8.8	0.029	0.638	1 vs.2: p = 0.102 1 vs.3: p = 0.032 2 vs.3: p = 0.022

SEM: standard deviation; F: test statistics, η^2: partial eta squared

A Shapiro-Wilk Test showed that repeated GRASSP strength and prehension scores, and pinch force follow a normal distribution.

Mauchly's test indicated that the assumption of sphericity has been met for GRASSP strength ($\chi^2(2)= 2.46$, $p = 0.078$), quantitative prehension ($\chi^2(2)= 0.22$, $p = 0.897$) scores.

*The assumption of sphericity for pinch force ($\chi^2(2)= 9.1$, $p = 0.011$) has been violated, therefore degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity for pinch force ($\varepsilon = 0.527$)

The upper extremity motor scores of all participants improved by up to eight points at the end of stimulation paired with training compared to two points or less following training alone (Table 4.5). Our third participant also converted from American Spinal Injury Association Impairment Scale (AIS) C to AIS D during stimulation treatment, and retained this improvement throughout follow-up.

Table 4.5 ISNCSCI examination scores throughout the study

Participant #		Baseline	Training	Stim+Training	Final follow-up
1	NLI, AIS (Motor Level Right | Left)	C5, B (C6 | C6)	C5, B (C6 | C6)	C5, B (C7 | C6)	C5, B (C7 | C6)
	UEMS Right | Left	12 | 12	12 | 12	14 | 12	14 | 12
	LEMS Right | Left	0 | 0	0 | 0	0 | 0	0 | 0
	Light touch | Pin prick	31 | 30	31 | 30	39 | 39	35 | 35
2	NLI, AIS (Motor Level Right | Left)	C5, B (C5 | C5)	C5, B (C5 | C5)	C5, B (C5 | C6)	C5, B (C5 | C6)
	UEMS Right | Left	9 | 10	9 | 11	12 | 14	12 | 13
	LEMS Right | Left	0 | 0	0 | 0	0 | 0	0 | 0
	Light touch | Pin prick	29 | 31	30 | 31	30 | 31	30 | 31
3	NLI, AIS (Motor Level Right | Left)	C5, C (C6 | T1)	C5, C (C6 | T1)	C5, D (C6 | T1)	C5, D (C6 | T1)
	UEMS Right | Left	14 | 24	14 | 24	20 | 25	20 | 25
	LEMS Right | Left	6 | 11	6 | 11	8 | 12	8 | 12
	Light touch | Pin prick	64 | 72	64 | 72	64 | 76	64 | 74
4	NLI, AIS (Motor Level Right | Left)	C5, D (C8 | C8)	C5, D (C8 | C8)	C5, D (C8 | T1)	C5, D (C8 | C8)
	UEMS Right | Left	19 | 23	21 | 23	22 | 24	21 | 24
	LEMS Right | Left	21 | 22	21 | 22	21 | 23	22 | 23
	Light touch | Pin prick	68 | 71	67 | 71	66 | 70	67 | 71
5	NLI, AIS (Motor Level Right | Left)	C5, C (C7 | C5)	C5, C (C7 | C5)	C5, C (C8 | C7)	C5, C (C7 | C6)
	UEMS Right | Left	19 | 17	19 | 17	21 | 20	21 | 19
	LEMS Right | Left	5 | 13	5 | 13	5 | 12	5 | 12
	Light touch | Pin prick	68 | 68	68 | 68	68 | 69	68 | 70
6	NLI, AIS (Motor Level Right | Left)	C3, D (C5 | C3)	C3, D (C5 | C3)	C3, D (C6 | C3)	C3, D (C6 | C3)
	UEMS Right | Left	16 | 12	16 | 12	20 | 16	20 | 15
	LEMS Right | Left	20 | 19	20 | 19	24 | 19	24 | 19
	Light touch | Pin prick	65 | 67	65 | 67	65 | 67	65 | 65

ISNCSCI: International Standards for Classification of Spinal Cord Injury
NLI: Neurologic Level of Injury
AIS: American Spinal Cord Injury Impairment Scale
UEMS: Upper Extremity Motor Score (0-50 points)
LEMS: Lower Extremity Motor Score (0-50 points)
Light touch and pin prick (each 0-112 points)

The benefits of non-invasive stimulation extended beyond restoration of hand and arm function to improvements in autonomic function. One participant's heart rate returned to normal after being bradycardic for 12 years. His heart rate was between 40 and 45 beats per minute (bpm) throughout the initial phases of the study. This made him feel dizzy and close to fainting early in the day. Beginning on the fourth day of stimulation, his resting heart rate gradually improved to a normal 60-65 bpm, which was maintained throughout the follow-up period. This participant also returned to sweating below his injury level, and thermoregulation was improved in three other participants. Two participants reported improvement in the quality of sleep due to the relief of disturbing night spasms. Participants 2 and 3, who used intermittent catheterization for bladder management, reported improved control of volitional voiding and decreased residual urine volume (Table 4.6). Moreover, one of the participants with motor complete injury and one with central cord syndrome pointed out that their core stability, balance control and lower extremity function improved during their routine exercise program, which was confirmed by their trainers.

Stimulation enabled functional recovery and allowed participants to resume their hobbies. Participant three resumed playing guitar for the first time in 12 years since his injury (Fig. 4.5a; Supplementary video 4.4). Participant four was able to return to oil painting five years after her injury (Fig. 4.5b). In parallel with functional improvements, psychological well-being, and physical health domains of WHO-QoL-BREF scores increased up to 19 points, and SCIM self-care domain improved by 1 to 4 points for each participant following treatment with stimulation (Table 4.6).

Table 4.6 Spasticity and quality of life scores

Participant		Baseline	Training	Stim+Training	Final follow-up
1	MAS UE Score	5	5	4	4
	WHO-QoL-BREF, Physical Health	56	75	81	69
	WHO-QoL-BREF, Psychological Well-Being	44	56	56	56
	SCIM III-Self Care	5	5	8	6
	SCIM III-Respiration and Sphincter management	15	16	17	17
2	MAS UE Score	6	6	6	6
	WHO-QoL-BREF, Physical Health	56	63	69	50
	WHO-QoL-BREF, Psychological Well-Being	75	81	81	69
	SCIM III-Self Care	0	0	2	2
	SCIM III-Respiration and Sphincter management	30	30	35	30
3	MAS UE Score	4	4	1	1
	WHO-QoL-BREF, Physical Health	56	56	75	75
	WHO-QoL-BREF, Psychological Well-Being	56	63	69	69
	SCIM III-Self Care	16	16	18	18
	SCIM III-Respiration and Sphincter management	33	33	34	34
4	MAS UE Score	9.5	9	7	8
	WHO-QoL-BREF, Physical Health	63	63	69	69
	WHO-QoL-BREF, Psychological Well-Being	69	75	81	81
	SCIM III-Self Care	7	7	8	10
	SCIM III-Respiration and Sphincter management	17	17	17	17
5	MAS UE Score	12.5	12.5	4.5	12.5
	WHO-QoL-BREF, Physical Health	44	44	56	56
	WHO-QoL-BREF, Psychological Well-Being	44	44	44	44
	SCIM III-Self Care	3	3	4	4
	SCIM III-Respiration and Sphincter management	15	15	16	16
6	MAS UE Score	21	18.5	14.5	16.5
	WHO-QoL-BREF, Physical Health	69	69	69	69
	WHO-QoL-BREF, Psychological Well-Being	63	63	81	75
	SCIM III-Self Care	1	1	5	5
	SCIM III-Respiration and Sphincter management	15	15	15	15

MAS UE Score: Modified Ashworth Scale Upper Extremity score (range 0-40 points, lower is better, see Methods); WHO-QoL-BREF: World Health Organization-Quality of Life-BREF Questionnaire (range 0-100); SCIM: Spinal Cord Injury Independence Measurement Questionnaire, Self-care (range 0-20 points); Respiration and Sphincter management (range 0-40 points)

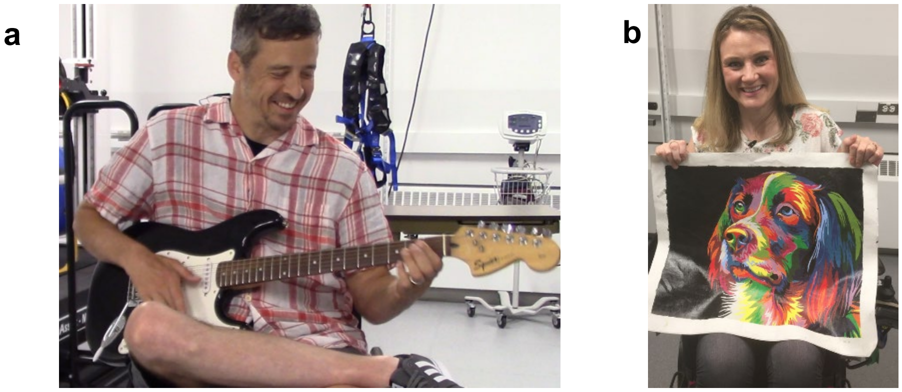

Figure 4.5. Improvement in fine motor skills Substantial functional improvement of the hands allowed participants to resume their hobbies for the first time since injury. a. Participant 3 was able to return to playing guitar for the first time in 12 years since injury (see also supplementary Video 4). His impairment category improved from AIS C to D following stimulation combined with training. b. Participant 4 with C5, AIS D, central cord syndrome returned to oil painting during the study which occurred five years after her injury.

4.5 Conclusion

Our findings demonstrate that transcutaneous spinal cord stimulation lead to both rapid and sustained recovery of hand and arm function for people with both motor complete and incomplete cervical spinal cord injury. The discovery that all functional improvements were maintained for many months beyond stimulation treatment is strong evidence for the induction of neuroplasticity within the central nervous system.

The unique combination of transcutaneous spinal stimulation and intensive training most likely enabled recovery via the following mechanism. Transcutaneous stimulation activates the spinal cord via sensory pathways in the dorsal roots to provide sub-threshold excitation to the interneurons and motor neurons within the spinal cord caudal to the lesion. Motor neurons closer to threshold are then more easily activated by remaining descending pathways from the brain, restoring volitional control of movement. The regained ability to move during stimulation enables people to participate actively in rehabilitation exercises, which leads to long-term recovery of function via neuroplasticity. Epidural stimulation likely activates similar sensory afferents pathway via the implanted stimulation electrodes, and a subset of studies are beginning to report that some functional gains persist beyond epidural stimulation. The non-invasive nature of transcutaneous spinal cord stimulation, however, can accelerate its translation to a clinical practice and restore long-term function to people with hand and arm paralysis.

4.6 Legends to the supplementary videos

Supplementary Video 4.1. Immediate effect of stimulation. Participant 3 had C5 level AIS C category injury 12 years prior to beginning the study. He was not using his right arm or hand for any daily activities. During training alone, function of his right hand did not improve. On the first day of stimulation, however, he was able to pick up, transport and release 3.8 cm balls easily.

Supplementary Video 4.2. Stimulation enables near-term and sustained improvement in precision grip. Prehension grip performance did not improve during 12 sessions of training alone. On the second day of stimulation, Participant 3 was not able to pinch 0.5-inch diameter marbles before the stimulator turned on. After a few minutes of stimulation, however, he was able to grasp, transport and release this size marble for the first time since his injury. The audio captures his reaction to this rapid improvement with biphasic stimulation at 45mA. Precision grip performance continued to improve, such that he could pick up small beads by the end of the stimulation treatment and even after 3-months of follow-up without further stimulation or training.

Supplementary Video 4.3. Illustration of reduced muscle tone and spasticity resulting from stimulation treatment. Participant 5 had C5, AIS C injury 2.5 years prior to beginning the study. High tone in her finger flexor muscles made it impossible to open her hand to grasp objects. Training alone did not reduce the muscle tone, and she was still unable to grasp 2.5cm wooden blocks. Starting from the first week of stimulation, the participant experienced gradual reduction of spasticity that allowed her to grasp and transport 2.5 cm blocks. Several days later, she could also grasp and release these blocks with much greater precision. Additional stimulation enabled her to open her fingers and thumb a greater distance to grasp ~7.5cm wooden pegs. This reduced spasticity and increased function was present both during and between stimulation sessions.

Supplementary Video 4.4. Stimulation restored fine motor skills of the paralyzed hand. Before the study, Participant 3 was not able to isolate and rapidly coordinate his left finger movements, and his right thumb could not move to strum the guitar. Stimulation paired with training restored his volitional control of thumb and individuated finger movements on both hands and motivated him to resume his hobby of playing the guitar for the first time since injury. This improvement in motor skills allowed him to depress the strings to the frets to rapidly form many musical cords. He continued to practice playing guitar throughout the study both with and without the stimulator active. His improved dexterity persisted for at least six months after stimulation.

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Author Contributions

F.I., C.P.H., and C.T.M. designed the study; F.I. determined and adjusted optimal stimulation parameters for each participant; C.P.H. performed the neurologic examination of the participants; F.I., L.N.B., and S.S. conducted intensive functional task training; F.I., and C.T.M. analyzed the data and prepared the manuscript.

Competing interests

The authors declare no competing interests.

Chapter 5 Conclusion

5.1 Summary of the dissertation

The work presented in this dissertation focuses on restoration of upper extremity function in individuals with tetraplegia. Despite the fact that hand and arm function is the highest treatment priority for people with tetraplegia, existing approaches are largely ineffective and rehabilitation interventions mainly focus on compensation for the loss rather than restoration. The aim of this research was to determine the efficacy of transcutaneous cervical spinal cord stimulation on recovery of volitional motor control as a novel neuromodulation strategy. Our findings demonstrate that non-invasive electrical spinal cord stimulation paired with intensive functional task training lead to both immediate and long-lasting recovery of upper limb function. People with both motor complete and incomplete injuries benefit from this combined intervention. Our discovery of long-lasting improvements persisting for months after treatment provide evidence for neuroplasticity enabled by the unique combination of these interventions.

In Chapter 2, we summarize the previous work on electrical stimulation. The discussions address early findings from animal studies and the translation of these findings into human studies. Human studies with epidural and transcutaneous stimulation show encouraging results for restoration of both locomotor and hand function. However, due to the relatively early stage of this emerging neuromodulation strategy and necessity of long-lasting intensive treatment periods, sample sizes in the studies are small. This limits generalizability of the findings to the heterogenous group of individuals with SCI. It is also important to recognize that optimal stimulation parameters remain to be determined.

In Chapter 3, the findings from the case study are presented. A three-phase, alternating intervention program delivered to a participant with C3 level AIS D category SCI. Results from one month of transcutaneous stimulation coupled with exercise therapy was compared to one month of exercise therapy alone. Combinatory treatment resulted in both dramatic and durable improvements in hand and arm function on all motor tasks measured. Outside of standardized test and measures, the participant experienced other improvements, such as reduction in residual urine volume and improved temperature regulation. This case study provided evidence that electrical neuromodulation of the cervical spinal cord combined with activity-based exercise therapy can promote substantial functional recovery of upper extremities in chronic SCI

Chapter 4 demonstrates the results of prospective, open-label, two arm study with an additional six participants. In this eight-months longitudinal study, following one month of weekly functional measurements, participants received two months intensive functional task training alone and two months transcutaneous spinal cord stimulation coupled with training. All six participants up to 12 years after injury, including two AIS B, two AIS C and two AIS D SCI, remarkably improved in their hand functions. Participants with motor complete injuries gained volitional thumb and finger movements for the first time since their injury. Restoration of volitional motor control enabled these participants to produce measurable pinch force. All participants retained functional gains for 3- to 6-month of follow-up without further stimulation or training. The magnitude of the improvements matched or exceeded previously reported results from surgically implanted stimulation. Transcutaneous spinal stimulation lead to improvements in autonomic functions, as well. Heart rate normalized in a participant who was suffering from bradycardia. Several participants reported improvements in bladder function, thermoregulation and normal sweating below the level of injury.

5.2 Contributions

This is the first study designed to investigate the efficacy of the unique combination of non-invasive spinal cord stimulation with intensive functional task training. To promote recovery of upper limb function in tetraplegia, we combined two critical drivers of neuroplasticity: neuromodulation and use-dependent plasticity.

The findings indicate that transcutaneous spinal stimulation improves upper extremity function in both motor complete and incomplete tetraplegics. Additionally, non-invasive stimulation enables volitional motor control and measurable force production of the hand muscles in motor complete individuals otherwise paralyzed. This result is in parallel and comparable with the findings obtained via surgically implanted epidural stimulation for volitional control the lower limb muscles.

The discovery of long-term recovery of hand and arm function without further stimulation provide strong evidence of neuroplasticity induced by transcutaneous spinal cord stimulation, even many years after injury. These durable improvement in hand function contributes to the quality of life, as shown by increase in WHO-QoL-BREF scores.

The findings of this study also provide significant information about it’s potential to improve cardiovascular dysfunction. One participant’s heart rate returned to normal after being bradycardic for 12 years. No serious adverse events were observed in seven participants throughout the study, suggesting that non-invasive spinal cord stimulation is a safe intervention.

Overall, the work presented in this dissertation provides evidence that transcutaneous spinal cord stimulation is a highly promising intervention for people with cervical spinal cord injury. The significant advantage of not requiring surgery can accelerate its translation to clinical practice to restore long-term function to people with hand and arm paralysis or paresis.

5.3 Future Directions

The work presented in this dissertation opens up questions for further research in order to improve its beneficial effects and to facilitate its translation to routine practice. Demystifying the mechanism of action is required to optimize the efficacy of transcutaneous spinal cord stimulation. The optimal stimulation parameters need be determined. Algorithms can be developed for customizing the frequency, pulse width, amplitude, location of electrode placement, and duration of stimulation.

Future studies with larger sample size are needed to test generalizability of the findings. Randomized controlled studies are warranted to evaluate the contribution of placebo effect. Additionally, non-invasive stimulation may not be beneficial for every individual with SCI. A tool can be developed to identify potential responders and non-responders, including neurophysiologic tests, imaging studies, or biomarkers.

The work presented in this dissertation shows the efficacy of transcutaneous spinal cord stimulation for participants in chronic stage, from 1.5 to 12 years after injury. Determining the optimal time window to start the treatment is another important goal to avoid learned non-use and to prevent maladaptive changes that occur after the injury.

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